- VOLUME D -

IN THE UNITED STATES DISTRICT COURT

IN AND FOR THE DISTRICT OF DELAWARE

PHARMACYCLICS LLC and JANSSEN BIOTECH, INC.,	:	**CIVIL ACTION**
Plaintiffs,	:	
vs.	:	
CIPLA LIMIGTED, et al..,	:	
Defendants.	:	**NO. 18-192 (CFC)**
----------	:	
PHARMACYCLICS LLC and JANSSEN BIOTECH, INC.,	:	**CIVIL ACTION**
Plaintiffs,	:	
vs.	:	
ALVOGEN PINE BROOK LLC and NATCO PHARMA,	:	
Defendants.	:	**NO. 18-275 (CFC)**

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Wilmington, Delaware
Friday, October 16, 2020
8:30 o'clock, a.m.

- - -

BEFORE: HONORABLE COLM F. CONNOLLY, U.S.D.C.J.

- - -

Valerie J. Gunning
Official Court Reporter

APPEARANCES:

MORRIS, NICHOLS, ARSHT & TUNNELL LLP
BY: JACK B. BLUMENFELD, ESQ. and
JEREMY A. TIGAN, ESQ.

Counsel for Plaintiffs

COVINGTON & BURLING LLP
BY: CHRISTOPHER SIPES, ESQ.,
ERICA N. ANDERSEN, ESQ.,
ALEXA HANSEN, ESQ.
BRIANNE BHARKHDA, ESQ. and
CHANSON CHANG, ESQ.
(Washington, D.C.)

Counsel for Plaintiff
Pharmacyclics LLC

KRAMER LEVIN NAFTALIS & FRANKEL
BY: IRENA ROYZMAN, ESQ.
(New York, New York)

Counsel for Plaintiff
Janssen Biotech, Inc.

HEYMAN ENERIO GATTUSO & HIRZEL LLP
BY: DOMINICK T. GATTUSO, ESQ.

-and-

APPEARANCES (Continued):

ALSTON & BIRD
BY: NATALIE CLAYTON, ESQ. and
(New York, New York)

-and-

ALSTON & BIRD
BY: SHRI ABHYANKAR, ESQ.
(Atlanta, Georgia)

Counsel for Defendants
Sandoz Inc. and Lek Pharmaceuticals d.d.i

YOUNG CONAWAY STARGATT & TAYLOR LLP.
BY: MELANIE SHARP, ESQ.

-and-

PROSKAUER ROSE
BY: SIEGMUND Y. GUTMAN, ESQ. and
DAVID MICHAEL HANNA, ESQ.
(Los Angeles, California)

Counsel for Defendants.
Alvogen Pine Brook LLC and Natco Pharma Ltd.

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P R O C E E D I N G S

(Proceedings commenced in the courtroom beginning at 8:30 a.m.)

THE COURT: All right. Good morning, everyone.

MS. ANDERSEN: Good morning.

THE COURT: I guess, Ms. Clayton, are you up first?

MS. CLAYTON: Yes, Your Honor. You asked us to confer on exhibits last night, so we have agreed upon them, ready to enter. I don't know if you want to do that now or later in the day?

THE COURT: Why don't we go ahead and do it now before we forget to take care of it.

MS. CLAYTON: For Dr. Steed, the exhibits the parties agreed were entered into evidence are DTX-1352, JTX-0322, JTX-1, DTX-2232, JTX-41, JTX-34, JTX-13, JTX-57, JTX-58, JTX-56, DTX-1307, DTX-1308, JTX-53, DTX-1304, DTX-2430, JTX-573, PTX-147 and JTX-506.

THE COURT: That's all agreed to?

MS. CLAYTON: Yes.

THE COURT: Go ahead.

MS. CLAYTON: For Mr. Goldman's deposition, the admitted exhibits are JTX-8, JTX-66, JTX-557, JTX-68,

JTX-551, JTX-69, JTX-73 and DTX-264. I thought they had agreed. I was told they have not formally responded yet.

THE COURT: Okay.

MS. BHARKHDA: I think we were still checking, because I believe Ms. Clayton may have missed, I believe, 507 was -- JTX- -- 506?

MS. CLAYTON: That was the last one I said.

MS. BHARKHDA: I'm sorry. I believe that's right. We will note for the record whether that's incorrect later in the day. I apologize. We were still checking.

THE COURT: All right.

MS. CLAYTON: For Ms. Dailey, it was just four exhibits, DTX-1266, DTX-1263, DTX-79 and DTX-1230.

MS. BHARKHDA: Your Honor, I don't believe that's correct. We only have three exhibits for Ms. Dailey. If you can let me pull it up. Not 1230.

MS. CLAYTON: 1230, Your Honor, is the actual deposition transcript.

MS. BHARKHDA: Your Honor, we don't think it's appropriate to enter the deposition transcript because we have clip reports. An entire deposition transcript, we have a general practice of entering those in the case. The deposition clips that were played will be in the record, but there's no cause for entering the entire deposition transcript.

THE COURT: Well, I do think we should have the transcript that was played.

MS. BHARKHDA: Correct.

THE COURT: We should not have any transcript for speaking that was not actually introduced in trial.

MS. CLAYTON: Understood, Your Honor. We misunderstood what the Court wanted in that record, so we can enter -- we will substitute those for, I guess, the clip reports or we could just excerpt the full transcript, whatever the Court finds easier to read.

THE COURT: I don't know what clip reports are. I just need a transcript, and, in fact, going forward, I also want a notebook. Ideally, I would have a notebook in front of me while the deposition is being played so I can read through that if you wanted going forward.

MS. CLAYTON: Yes.

THE COURT: That's what needs to be put in the record.

MS. CLAYTON: Okay. We'll come into agreement on the excerpts to the transcript for DTX-264 and DTX-1230 that should come in the record and were played at trial and resubmit that to the Court.

THE COURT: Right. Okay.

MS. BHARKHDA: Your Honor, I believe there were some left off from Mr. Goldman as well. DTX-264, DTX-67,

DTX-546 and JTX-1.

MS. CLAYTON: No objection, Your Honor.

THE COURT: All right. Does that take care of all of the exhibits from yesterday?

MS. BHARKHDA: I think we're still conferring on Mr. Steed to make sure our list aligns with defendants'.

THE COURT: All right.

MS. CLAYTON: I believe Alvogen had some exhibits to enter from Dr. Swift. Is that right?

THE COURT: Let's do that.

MR. GUTMAN: Yes Your Honor. We conferred with plaintiffs and have an agreement regarding the exhibits. We're getting those printed out currently that were agreed upon. Perhaps just before the next break we can move those into evidence.

THE COURT: That sounds good.

MR. GUTMAN: Your Honor.

THE COURT: All right. Any other housekeeping before we start? No? Okay. Who is next then?

MS. CLAYTON: Your Honor, we're going to play two more deposition clips this morning. The first is Dr. Smyth.

I believe plaintiffs have the same objection to Dr. Smyth as they did for Mr. Goldman yesterday, but I hope we can come to the same resolution, because they're just

inventorship. We can discuss at a later date the issue plaintiffs have related to their argument, which we disagree with, that the theory was late.

MS. BHARKHDA: Correct, Your Honor. We have the same objection with respect to the inventorship theory. With respect to both Mr. Smyth and Mr. Wirth whose depositions will be played this morning, we have no problem with the proposal that we reserve our objection now and we can proceed with playing the clips and save the objections for later.

THE COURT: All right. We'll do that. Hold on one second.

MS. CLAYTON: Your Honor, I believe you should have a binder with Dr. Smyth's transcript in it that we had delivered to the Court. There should be a clip report, Your Honor, in the pocket of the portions we're going to play.

THE COURT: Sounds good. Thank you very much.

Ms. Bharkhda, did you have anything else you wand to add?

MS. BHARKHDA: I don't believe so.

MS. CLAYTON: Your Honor, at this time defendants will play the deposition of Dr. Mark Smyth. He is a named inventor on both the '548 and the '231 patents.

He was deposed by defendants on November 21st, 2019, at which time he was employed by Pharmacyclics.

You will hear 57 minutes and 24 second of his deposition testimony. Thirty minutes and 48 second will be charged to defendant and 26 minutes and 36 seconds will be charged to plaintiff.

MR. ABHYANKAR: And, again, Your Honor, this would be for the inventor of the '455 patent as well.

THE COURT: Okay. Off the record.

(Discussion held off the record.)

THE COURT: We're back the on record. Let's play the deposition. Thank you.

(The videotaped deposition of Dr. Mark Smyth was played as follows.)

"Question: Good morning, Dr. Smyth.

My name is Jayita Guhaniyogi, and I am from the Kasowitz firm. I represent the Zydus defendants in this case and I will be asking you some questions today followed by -- some of my co-counsel might ask you some questions later.

"Could you please state your full name for the record?

"Answer: Mark Steven Smyth.

"Question: Who is your current employer?

"Answer: Pharmacyclics.

"Question: If you start with -- in 1984 you received a bachelor's degree in chemistry from Indiana

University of Pennsylvania; correct?

"Answer: Correct.

"Question: That degree -- that was chemistry; correct?

"Answer: Yes.

"Question: After your bachelor's degree, according to your C.V., Exhibit 2, you received a Ph.D in 1989 in synthetic organic chemistry from the State University at New York at Buffalo; correct?

"Answer: Yes.

"Question: After 2007, after you left Proteolix, you joined Pharmacyclics; is that correct? In 2007?

"Answer: Yes. Correct.

"Question: What month was that? Do you recall?

"Answer: November 2007.

"Question: Okay. When you joined Pharmacyclics in November 2007, you joined as a principal scientist in the process chemistry department of Pharmacyclics; is that correct?

"Answer: Correct.

"Question: What was your role when you joined as a principal scientist in process chemistry at Pharmacyclics?

"Answer: I was responsible for all technical

aspects of the ongoing development projects; so I was lead scientist.

"Question: What type of development projects that you were involved in when you joined as the principal scientist?

"Answer: We were working on chemical development of a factor VIIa inhibitor, the protease tyrosine kinase inhibitor, and the h-stack inhibitor programs.

"Question: When you say that you were responsible for all technical aspects of the ongoing development projects, what do you mean by all technical aspects?

"Answer? I was responsible for all the chemistry activities related to those programs -- from lab work, up through manufacturing.

"Question: Okay. As part of your role as the project leader, were you involved as a polymorph analysis at Pharmacyclics?

"Answer: Yes.

"Question: What did that involve?

"Answer: Can you be more specific, please?

"Question: What did your role in polymorph analysis involve when you were project leader at -- when you were principal scientist at Pharmacyclics?

"Answer: I was responsible for setting up and leading the technical interactions with a third party -- with the CMO that we had worked with and then, also, with a third party analysis lab.

"Question: Did anybody in your team in Pharmacyclics run polymorph analysis?

"Answer: Not in-house, no.

"Question: Okay. You were collaborating with the third party, the manufacturing -- the contract manufacturer and the third-party analysis lab; correct? On polymorph analysis?

"Answer: I was working with the two parties. Yes.

"Question: You were reviewing their reports; is that correct?

"Answer: Yes.

"Question: When you joined Pharmacyclics in 2007, as part of the BTK project, did that involve the ibrutinib project?

"Answer: Yes.

"Question: The involvement you had with the third party contract manufacturing organization and the third-party analysis lab at that time you were a principal scientist when you signed Pharmacyclics -- can you elaborate on your role on that collaboration on polymorphic analysis?

"Answer: My role was to identify and set up a collaboration with an external party to perform analysis of materials we had generated, as well as to conduct additional studies for further understanding of the solid state properties of the materials we were preparing.

"Question: When you say your role was to identify, were you involved in the identification of the third party analysis lab who were involved in the polymorph analysis of the projects that you were working on at that time?

"Answer: Yes.

"Question: When you were promoted between 2010 and 2012, according to your C.V. Exhibit 2, you were promoted to director of process development and manufacturing at Pharmacyclics; correct?

"Answer: Correct.

"Question: How did your role change at that time?

"Answer: I had -- I continued on as the technical lead on all the programs we were working on, as well as I had hired a couple of process chemists that I was in charge of their day to day operational functions.

"Question: Progressing to when you -- in 2012, according to your C.V., you got promoted to a senior director of process development and manufacturing at

Pharmacyclics between 2012 and 2014; is that right?

"Answer: Yes.

"Question: How did your role change when you became senior director of process development and manufacturing?

"Answer: Increased responsibilities for external activities of manufacturing of API.

"Question: Did that role involve polymorph analysis of the API -- of API that you were involved in?

"Answer: Yes, it included that.

"Question: Were you involved in any collaboration with third-party analysis labs on polymorph analysis?

"Answer: Yes.

"Question: Did anybody on your team perform polymorph analysis at Pharmacyclics?

"Answer: No.

"Question: Okay. Focusing on particularly your work on ibrutinib projects -- ibrutinib, i-b-r-u-t-i-n-i-b, I think you said earlier that when you joined Pharmacyclics in 2007.

"Is that when you also started working on the ibrutinib project?

"Answer: Yes.

"Question: Okay. November 2007 is when you

started working on the ibrutinib project?

"Answer: Yes.

"Question: On that project, particularly on the ibrutinib project, what were your responsibilities when you joined as a principal scientist back in 2007 -- November of 2007?

"Answer: My job was to take the lead role in the scientific and technical discussions with our third party manufacturer who was doing the development work.

"Question: What was the name of the third-party manufacturer at that time you joined?

"Answer: Seres Laboratories.

"Question: If I refer to Seres, you understand I am referring to the same third party?

"Answer: Yes.

"Question: When you joined November 2007, was Seres also identified and engaged as the third-party contract manufacturer for Pharmacyclics on ibrutinib?

"Answer: Yes.

"Question: When did you first get involved with polymorph analysis of ibrutinib after you joined in November 2007? Joined Pharmacyclics?

"Answer: It was early 2008.

"Question: What did that role involving polymorph analysis of ibrutinib involve when you started the

analysis in early 2008?

"Answer: Working with the third-party manufacturer, we had encountered different solid forms and materials that were behaving differently than what we expected when he was examining a recrystallization process, and this led to a realization that -- and the discovery that we had these different polymorphic forms that needed to have some analysis performed.

"Question: When you say the third-party manufacturer, you are referring to he was examining a recrystallization process, who specifically are you referring to?

"Answer: Dr. David Wirth.

"Question: Dr. David Wirth was from Seres?

"Answer: He worked at Seres, yes.

"Question: Was Dr. David Wirth your primary contact at Seres?

"Answer: Yes.

"Question: Who directed Dr. David Wirth to examine the recrystallization process at Seres?

"Answer: Me.

"Question: I am going to hand you what has been marked as Smyth Exhibit 3, a document bearing production numbers, and, Dr. Smyth, by production numbers, I am referring to these numbers that have been stamped at the

bottom of each page on the right-hand side, which we call Bates numbers:

"The production number IMBPCYC05002488 to IMBPCYCO5002482.

"Question: Dr. Smyth, do you recognize Exhibit 3?

"Answer: Yes.

"Question: If you turn over from the -- on the first page it says No. 678; correct?

"Answer: It says that, yes.

"Question: If you turn it over, on the second page it says assigned to and that is a handwritten name. Mark S. Smyth; is that right?

"Answer: Correct.

"Question: That's you; correct?

"Answer: Yes.

"Question: Does this lab notebook between the dates that we just went through -- 26 November of 2017 to April 27, 2010, -- does this time period reflected in the lab notebook accurately reflect the work that you personally performed in the lab on the BTK project?"

THE COURT: All right. Can we stop for a second? Can we stop this for a second?

I don't see this exhibit in the notebook I have. Maybe it is, but I'm at a loss to see it.

I don't see this exhibit in the notebook that I have that has been identified as Smyth deposition testimony. What is the exhibit?

MR. ABHYANKAR: Which exhibit is it? One second, Your Honor. Sorry.

(Pause.)

MR. ABHYANKAR: Your Honor, I think what happened is the affirmative designations from defendants, those are the exhibits we prepared to send to the Court. This may be an exhibit that was designated by plaintiff in their counters, but we can try and get that exhibit over to you as soon as possible.

MS. BHARKHDA: Your Honor, I apologize. We understood the parties that were submitting the binders were going to include all of the appropriate exhibits, so we will make sure that you have them. I apologize.

THE COURT: Okay.

MS. BHARKHDA: We thought the party offering the testimony was going to include them.

THE COURT: How many more exhibits are we talking about that aren't going to be in the notebook?

MR. ABHYANKAR: Your Honor, I will have to check on that to compare, because I just have the list in front of me that we identified for admission into evidence after the deposition was over, but I can get that to you quickly.

THE COURT: All right. So I think what we should do is maybe stop this deposition and move on to something else because I don't think it's fair to plaintiffs that I don't get to see the exhibits as I'm listening to his deposition.

MR. ABHYANKAR: Understood.

THE COURT: So I guess, Sandoz, why don't you adjust and we'll come back to it. What's next?

MR. ABHYANKAR: Okay. Your Honor, the next deposition is Mr. Wirth, but I believe that we may have the same issue for Mr. Wirth. Not all of the exhibits are going to be in the binder that is with a sent to the Court this morning.

I believe after Mr. Wirth is Mr. Hostetler. Is that correct? Okay. And that is going to be played by Alvogen's counsel, so I don't know, Mr. Hanna, if you have you sent all of the exhibits for that witness?

MR. HANNA: Yes. I understand, Your Honor, you should have the exhibits for Mr., Dr. Hostetler.

THE COURT: And that would be for both sides since we're playing the joint transcript. Right?

MR. HANNA: Yes. That's my understanding.

THE COURT: All right. Just so you'll know, I've got a notebook that was Hostetler deposition, Hostetler clips. It has DTX-01 and DTX-1436. That's it. There are

just two exhibits discussed in Hostetler?

MR. HANNA: That's correct. I don't think there are any for plaintiffs for this one.

THE COURT: All right. Let's move on. We'll play Hostetler.

MR. HANNA: Thank you, Your Honor. And Dr. Hostetler, he is an attorney who prosecuted the compound patents, for example, the '309 patent and the '444 patent for context.

THE COURT: All right. Thank you, Mr. Hanna.

Ms. Bharkhda, did you have something? You were at the mike.

MS. BHARKHDA: No, Your Honor.

THE COURT: Maybe you can figure out how to get me these things. I don't know how many exhibits you're talking about. You can print them out maybe, but I don't think it's fair.

Going forward, if you're going to be the person presenting a joint deposition, you've got to present both sides in the notebook of all of the exhibits.

MS. BHARKHDA: Your Honor, may I ask, is Sandoz preparing the missing exhibits now?

THE COURT: I do think the burden is on Sandoz.

MR. HANNA: We are. Just so Your Honor

knows, the next deposition after Dr. Hostetler, for Mr. Wirth, there's only one exhibit is our understanding, and Brianne, you can confirm. That one we can play and you will have that exhibit and we'll work on the Smyth missing exhibits.

THE COURT: Okay. And when it comes to Wirth, like I said, somebody can e-mail chambers. I don't know how long this exhibit is, but if it's not unduly lengthy, you can print it out. All right?

So let's do Hostetler. Thanks.

(The videotaped deposition of Dr. Michael Jon Hostetler was played as follows.)

"Question: Can you state your full name for the record, please?

"Answer: Michael Jon -- it's J-o-n -- Hostetler. My primary office is in the South of Market, or SoMa office, in San Francisco. I am also listed as being in the San Diego office.

"MR. GUTMAN: Thank you. I'll ask the court reporter to mark as Hostetler Exhibit 6 -- I'm sorry. Exhibit 3. I apologize -- a document bearing Bates numbers IMBPCYC04444954 through -028 or -5028. Sorry. And it's a U.S. Patent No. 7,514,444.

"Question: Do you recognize Exhibit 3?

"Answer: I'm assuming this is a complete copy,

or should I look through it?

"Question: I believe it's a complete copy. That's how it was produced to us.

"Answer: I see a document, U.S. Patent 7,514,444. I could take the time to look through it to make sure that it's a complete copy; but other than that, I recognize it as U.S. Patent 7,514,444.

"Question: Did you -- were you involved in prosecuting and obtaining issuance of -- if we called this the '444 patent, will you understand what I mean?

"Answer: I will understand what you mean, Dr. Gutman.

"Question: Okay. Were you involved in obtaining the issuance of the '444 patent that is Exhibit 3?

"Answer: I was involved in the prosecution of the patent application and the issuance of the '444 patent.

"Question: Okay. And what do you mean by the 'physical form of a structure'?

"Answer: The physical form of a structure is very broad. It's how it appears. And it could be everything from a gas, a liquid, a solid, an amorphous material, a crystalline material. It would refer to something that's in a bottle. It can refer to something as it's dissolved in a solution. It's whatever physical form that it takes.

"The word 'compound' is interchangeable with both chemical structure and the physical form of -- of -- of a material.

"Question: And so what did you intend to convey when you wrote, a compound of formula D having the structure depicted in claim 1?

"Answer: As I mentioned before, a compound refers to a chemical's structure as well as a physical form that that material is present. It's -- it's -- the term is -- refers to both the chemical, and the physical aspect of that chemical.

"Question: So is it your testimony that you intended claim 1 to cover all physical forms?

"Answer: All physical forms of compounds having the structure of formula D. Yeah. All physical forms. Correct.

"Question: So it's your testimony that the compound of claim 1, as you wrote it, as you understood what you were writing, covers amorphous forms of the compound having formula D. Correct?

"Answer: Covers -- claim 1 covers the amorphous forms of -- of compounds having the structure of formula D. Yes.

"Question: And I think you also mentioned that it's -- it was your intent as you wrote claim 1 that it

would cover crystalline forms also of the compound having formula D. Correct?

"Answer: It covers compound -- claim 1 covers crystalline forms of compounds having the structure of formula D.

MR. GUTMAN: I will ask the court reporter to mark as Exhibit 23 a document bearing Bates Numbers IMBPCYC00035120 through 145.

"Question: And can you identify Exhibit 23 for me, Dr. Hostetler?

"Answer: I recognize Exhibit 23 as a response to a non-final office action dated July -- on June 11th, 2015 for the '949 patent application that I filed and signed electronically on August 24th, 2015.

"Question: And this is responding to the office action that is Exhibit 22. Correct?

"Answer: Yes, that is correct.

"Question: And starting on the page ending with Bates number 5129 and continuing through 5132, you address the -- you respond to the double patenting rejection based on the '444 patent that was provided in the office action that is Exhibit 22. Correct?

"Answer: I will review that and tell you. Question.

So, Dr. Gutman, starting at the bottom of Bates

number 129 versus double patenting rejections, through what appears to be Bates number 132, bottom of the first full paragraph -- that's all based on the foregoing reasons, that appears to be where I address the double patenting rejection of the '444 patent.

"Question: That wasn't my question. My question was whether you believe, in view of the statement that you made here, that the '444 patent claims are enabled with respect to polymorphs of the disclosed compound.

"Answer: As a polymorph is a type of physical form of the -- the category of -- the category of physical forms is enabled in the '444 patent for compounds of formula D. And I believe it is my view that it is enabled.

This is a slightly different statement here. In fact, it's a substantially different statement here in regards to enablement of the '444 -- the '444 patent, in terms of polymorphs.

"Question: So it's your testimony that the '444 patent claims are enabled with respect to polymorphs? Is that your testimony?

"Answer: It's enabled in terms of -- compounds of formula D, including structure -- I mean, physical forms of formula D; and that includes polymorphs.

"Question: Well, I'm not asking you to change your answer. I'm asking you to respond to my question,

which you haven't yet done. So let me try it again.

"I'm not asking you whether the '444 patent claims are enabled broadly, I'm asking you whether -- in view of the statement you made here, whether it's your understanding that the '444 -- '444 patent claims are enabled with respect to specifically polymorphs of the disclosed compound that's referenced here.

"Answer: One of skill in the art would not be able to predict what the polymorphs of that compound would look like. And that is different from whether or not it is enabled to make or use physical forms, including polymorphs of that compound."

(End of videotaped deposition.)

THE COURT: All right.

MR. ABHYANKAR: Your Honor. And we're working on the slides. I think the disconnect was that plaintiffs didn't identify what exhibits they had countered with, so we're pulling those and we'll send them over to the Court as soon as possible.

We'll move on to the deposition of Mr. David Wirth. He is a named inventor on both the '548 and the '231 patents asserted against Alvogen.

He was deposed by defendants October 30th, 2019. You'll hear 34 minutes and four seconds of his deposition testimony. Seventeen minutes and 26 seconds will be charged

to defendant and 15 minutes and 38 seconds will be charged to plaintiff. And you should have one exhibit, JTX-8, Your Honor.

THE COURT: All right. Before you do that, why don't each side put a lawyer up and explain to me the significance of the deposition testimony I just heard.

MR. ABHYANKAR: I believe that was Alvogen's witness.

THE COURT: But I'm going to want somebody from plaintiffs to respond. All right. Briefly, Mr. Gutman. What was the significance of what I just heard?

MR. GUTMAN: I apologize, Your Honor. I was on mute.

THE COURT: That's okay.

MR. GUTMAN: I think it has broad significance. You may recall yesterday we were talking about whether Pollyea was enabled for polymorphs. The '444 patent is prior art that was available prior to the crystalline form patents. It's the compound patent.

You may recall from the opening statement that we provided that the compound patents were filed earlier and published before the filing date of the crystalline form patents, and so this is significant to whether crystalline forms and polymorphs were actually enabled prior to the filing date of the crystalline form patents.

So that issue impacts a few issues in the case. One is --

THE COURT: So, wait. So you are saying -- so what is the one-sentence summary here of the testimony is that the '444 patent claims enable what?

MR. GUTMAN: Polymorphs of ibrutinib which contributes to the obviousness of the crystalline form patents.

THE COURT: Okay.

MR. GUTMAN: Because -- and also helps establish that the prior art references that we're relying on as anticipatory under the theory of inherency were enabled as of the time, of the relevant time period.

THE COURT: And is it your position that the '444 patent enabled all polymorphs of ibrutinib?

MR. GUTMAN: I think that's what Dr. Hostetler testified to, Your Honor.

THE COURT: Okay.

MR. GUTMAN: So, yes. Our position is that it enabled, and I think it's plaintiffs' position that it enabled all polymorphs, including form A.

THE COURT: Okay. All right. Thank you.

Ms. Bharkhda?

MS. BHARKHDA: Your Honor, we don't actually think that his testimony has any relevance to any issue in

the case. The '444 patent is not asserted in the case. Alvogen is not relying on the '444 patent as an anticipatory reference. We don't think it's highly relevant. Also, I think it's an improper attempt to use prosecution counsel's opinion as an attempt to get in some kind of expert testimony that's improper expert testimony.

And --

THE COURT: Hold on. There's no objection to the term.

MS. BHARKHDA: We didn't because we don't think it's relevant.

THE COURT: Okay. But, you know, that objection was waived to the extent that its expert said it's inappropriate because it touches on anything. The only objection -- frankly, I don't think you -- I don't remember you voicing a relevance objection. I don't think there has been an objection to the admission of this testimony.

MS. BHARKHDA: We didn't. We didn't object to it. We just don't think it has any bearing on any issue.

THE COURT: Let me ask you this: Do you agree that the '444 patent enables all polymorphs of ibrutinib?

MS. BHARKHDA: I don't think that is a proper phrasing of the inquiry.

THE COURT: Okay.

MS. BHARKHDA: The question is whether the '444 patent enabled the compound that it claims and we believe it enables the compounds in all physical forms.

THE COURT: All right.

MS. BHARKHDA: That does not mean it discloses any polymorph or enables particular polymorphs. It is not directed to crystalline forms or polymorphs of ibrutinib. It is directed to --

THE COURT: That's not my question. Just answer the question. Whether you think it's relevant or whether it's the right inquiry or not, does the '444 patent enable all forms, all polymorphs of ibrutinib?

MS. BHARKHDA: No, Your Honor.

THE COURT: Why not?

MS. BHARKHDA: Because it -- that's not the subject matter of the claim. It enables the compounds that are in the claims and it does not disclose all polymorphic forms or any for that matter polymorphic forms.

THE COURT: Okay. Thank you. All right.

Thank you, counsel. Anything else? We'll go with the next one.

MR. GUTMAN: Thank you, Your Honor.

MR. ABHYANKAR: So, Your Honor, we'll begin the deposition of Mr. Wirth now, which I said will last about 34 minutes and four seconds.

THE COURT: Okay. This one -- wait. Sorry. And I apologize. You probably said this, sir, before. I do have all the exhibits for this now?

MR. ABHYANKAR: You do. There's actually only one, JTX-8. It's the '753 patent.

THE COURT: Thank you very much. I apologize I had to ask that question again. Go ahead.

MR. ABHYANKAR: No problem.

(The videotaped deposition of David Dale Wirth was played as follows.)

"Question: Could you please state your full name for the record?

"Answer: David Dale Wirth.

"Question: What was your graduate degree in?

"Answer: Chemistry.

"Question: Okay. And did you have a particular specialty in chemistry?

"Answer: Organic chemistry.

"Question: Okay. Did you receive a Ph.D.?

"Answer: Yes.

"Question: In organic chemistry?

"Answer: Yes.

"Question: As part of your graduate work, did you have experience working with polymorphic forms of compounds?

"Answer: No.

"Question: Any experience working with formulations, pharmaceutical formulations?

"Answer: In graduate school you mean?

"Question: Uh-hum.

"Answer: No.

"Question: Okay. Did you ever receive a medical degree?

"Answer: No.

"Question: Okay. After graduate school, what did you do?

"Answer: I did some post-doctoral research.

"Question: And where did you do that?

"Answer: Dartmouth College.

"Question: Okay.and at what -- when was that? When did you conduct this post-doctoral research?

"Answer: So began in the fall of 1980 through all or most of the following year, 1981.

"Question: What did you do after your post-doctoral research at Dartmouth?

"Answer: Then I accepted a position at Eli Lilly and Company.

"Question: At -- when was that, approximately?

"Answer: It began January 1982.

"Question: Okay. And where did you get -- get

your job in California?

"Answer: So I was employed by Seres Laboratories in Santa Rosa.

"Question: What is Seres Laboratories?

"Answer: Seres Laboratories was a small development and manufacturing company that worked with -- in the pharmaceutical area, basically.

"Question: And what was your role at Seres when you joined?

"Answer: I was I believe the title was director, director of chemistry or director of laboratory operations, one of those wordings.

"Question: And what were -- what were your responsibilities as director of chemistry at Seres?

"Answer. So the -- the working chemists that worked in the laboratory reported to me. So there was some management kind of responsibility for the other chemists. Then I was also responsible for doing chemistry. Actually did chemistry in the laboratory. And I was responsible for interactions with clients as well.

"Question: What types of projects did you do at Seres?

"Answer: The projects were of the development and the manufacturing, really, of intermediates and active drug substances.

"Question: And what specifically did you do to assist with the development and manufacturing of intermediates and active drug substances at Seres?

"Answer: So all the things I just mentioned, such as working with the clients to discern what was needed, what the project goals were. And then working with the rest of the chemists and the staff to decide who was going to perform those activities and make some assignments with respect to responsibilities and activities that we were going to do. And I performed some laboratory work myself.

"Question: Or -- or, you know, that you used third parties to run specific tests for projects that you were asked to assist with from your clients?

"Answer: We did use some external analytical laboratories, yes.

"Question: Okay. Did Seres have the capability to run XRD analysis on a compound?

"Answer: No, we had no X-ray capabilities.

"Question: Were you ever involved in running an XRD test for a compound when you were at Seres?

"Answer: I -- I did not run the instruments myself.

"Question: Did you direct others to run XRD analyses for your clients while you were at Seres?

"Answer: So this was done by external laboratories. So there was, yes, direction sent to the external laboratory to run a sample.

"Question: Right.

But you didn't provide direction on how to run the sample, correct?

"Answer: No.

"Question: Okay. Have you ever run an XRD analysis, just generally?

"Answer: In terms of using the instrument myself?

"Question: Uh-hmm.

"Answer: No.

"Question: All right. So after Seres -- or when did you leave series?

"Answer: It was early in the year 2010.

"Question: Are there -- are there known solvents that are traditionally used to discern whether you have a crystal or not?

"Answer: So I don't really know what people traditionally use. It was your word. What I use, I -- I have experience with a -- with designing the solvent system based upon the particular task, meaning that every molecule is different because it's different in structure.

And you often have different goals in mind. So

there's -- there's no list that I would use over and over, typically, because of that.

"Question. Dr. Wirth, before the break we were talking about your time at Seres.

"Are you familiar with ibrutinib?

"Answer: Yes.

"Question: Okay. And how are you familiar with ibrutinib?

"Answer: It's -- it's a compound with the name -- that name was adopted after I worked on it, but I know it -- now that it does have that name. At the time when I was at Seres, we worked on that molecule, which we knew by the number, not -- not that name, right.

"Question: Right.

"Do you recall when you first became aware of that, the ibrutinib molecule?

"Answer: It was shortly after I joined Seres. So it was, I believe, in -- in -- some time during '06 or -- or early '07, in that time frame.

"Question: How -- how did you become aware of the molecule?

"Answer: So we were approached -- the company, Seres, was approached by people from Pharmacyclics with a -- a request. We typically call these requests for a proposal. Basically they asked us to evaluate the chemistry and decide

if we could provide a quote to -- you know, to provide services to them.

"So that's how we first heard of the molecule, I think.

"Question: And when you say they asked you to evaluate the chemistry, what specifically did they ask you to do?

"Answer: So they presented us with some of their -- their goals, meaning that they needed some material made, they needed some -- they needed process chemistry and process development. And ultimately they needed manufacturing, but probably in -- in phases, some initially and then some later, potentially.

"So in the -- in the initial discussion, I don't remember whether it -- we included all of those or whether we really just talked about the chemistry. They were primarily interested in process chemistry, making manufacturable processes.

"Question: What information did Pharmacyclics provide you at the outset?

"Answer: About this molecule?

"Question: Or about the molecule in asking you to help evaluate the chemistry.

"Answer: So they provided either initially or after the contract -- I'm not sure when this came -- but the

data that they would -- they provided was really experimental procedures that had been used earlier in -- within Pharmacyclics to prepare the molecule, basically. Experimental procedures was primarily where -- the information that we got.

"Question: Did Pharmacyclics ask -- ask you to evaluate their synthetic route and improve it?

"Answer: Yes.

"Question: Okay. Did they ask you to do anything else?

"Answer: Yes. But I don't -- again, it was in stages. So there were -- because they ultimately needed material delivered as well.

"Question: Who was your main point of contact at Pharmacyclics on the Ibrutinib project?

"Answer: Mark Smyth.

"Question: What was Mark Smyth's role in the ibrutinib project?

"Answer: My understanding was that Mark was the -- in charge of the process chemistry.

"Question: How was he in charge of the process chemistry?

"Answer: By -- as -- as we just said, his -- his interaction then with us was to manage -- manage the process chemistry, and he was the key person that interacted

with -- with me at Seres. So from the standpoint that we were doing process research and process chemistry, that seemed to be his function, as I understand it, at Pharmacyclics.

"Question: Are you familiar with a lab called SSCI?

"Answer: I am.

"Question: Okay. Who is SSCI?

"Answer: They're a solid state chemistry firm located in West Lafayette, Indiana.

"Question: Did you ever use them as part of your work at Seres?

"Answer: So I -- I do not specifically recall which laboratory we used. I -- my recollection was that we did send samples to a solid state chemistry laboratory. But I -- I cannot remember which laboratory we used.

"Question: Okay. All right. Well, do you remember why you sent samples to a solid state chemistry laboratory?

"Answer: Yes. We -- we were asking -- we were having analysis done to determine the -- really the crystal form of the materials that we had.

"Question: With respect to the ibrutinib project?

"Answer: Yes.

"Question: Okay. And why were you doing that?

"Answer: As part of the development of a drug substance, it's important to understand what solid state form you have to characterize the -- the drug substance that you have as fully as you can. And that's one of the things that is wise to do, in my opinion, to discern whether the material you have is crystalline or not crystalline. And then if it is crystalline, to record, you know, the characteristics of it, such as its XRPD pattern and just to fully characterize the material that you have.

"As part of the ibrutinib project, you, yourself, did not characterize the crystalline form of the ibrutinib molecule that you received from Pharmacyclics?

"Answer: The compound that we received from Pharmacyclics is what you're asking?

"Question: Uh-hmm.

"Answer: I did not characterize that.

"Question: Okay. You sent -- you sent some samples to the third-party lab, right?

"Answer: We did.

"Question: Okay. Which samples were those?

"Answer: Those were samples that I had produced in the laboratory.

"Question: Were they labeled with a -- with a number or some sort of designation?

"Answer: I certainly don't recall specifically what any one was, but the practice was to label them with the notebook number from -- that describes their preparation. So any sample that went out would have had a -- a notebook number assigned to it and affixed to the label.

"Question: All right. Do you recall what types of analytical tests were run by the third-party lab in determining the crystalline form of the samples that you prepared?

"Answer: I -- I recall that XRPD was our -- was of our primary interest, and so we certainly had that test run.

"Question: Just to confirm, you had nothing to do with the formulation or the -- the -- the design of the making of a formulation of the capsule itself, correct?

"Answer: No. My only involvement was producing the drug substance that was used.

"Question: Dr. Wirth, I've handed you what's -- of you've been handed what's been marked as Defendants' Exhibit 5. If you could take a look at it. This is a copy of U.S. Patent 9,296,753.

"Answer: Okay.

"Question: All right. Have you seen this patent before?

"Answer: Yes.

"Question: If you turn to the second page, you see under inventors it lists Mark Smyth, Erik Goldman, yourself and Norbert Purro.

"Do you see that?

"Answer: Yes.

"Question: So you were listed as a named inventor of this patent?

"Answer: Yes.

"Question: All right. Are you, in fact, an inventor on this patent?

"Answer: Yes.

"Question: Okay. And what -- what is -- what were your contributions to this patent as far as the invention is concerned?

"Answer: So my contribution was in the -- in the initial discovery and isolation of some polymorphic forms of this compound.

"Question: What did you do to discover or isolate polymorphic forms of the compound that is claimed in the patent?

"Answer: So I designed some laboratory experiments and executed some laboratory experiments to -- to try to crystallize the compound and was successful in crystallizing the compound. And then those were -- were

analyzed externally. And it was, in fact, found that they were crystalline.

"Question: Right.

"You said that your contribution was the discovery and isolation of polymorphic forms of the compound. Any specific polymorphic forms?

"Answer: So I'm not -- I'm not clear on how many of the polymorphic forms I actually discovered. I -- I do believe that at least one of them -- well, at a minimum, one, but there -- there seemed to be several here that -- that are in the examples. And there were several that I found.

"Question: So you're not clear on how -- on the -- how many of the polymorphic forms you discovered, but there were several that you found; is that your testimony?

"Answer: So the -- I think several is probably an incorrect word since what -- what you have refreshed my memory from looking at the prior reports was that we had two forms in particular, which is what I do recall, that there were two forms that had been found and that we had -- we were dealing with those particular batches that we reviewed. So my memory is that I was working primarily with two forms.

"Question: What forms were those?

"Answer: So those were the forms that -- one was the high melting form, 155, roughly, melting form that was in this document is -- appears to be called form A and in this report was called form A.

"Question: And what was the other form?

"Answer: It was referred to as B, I think, lower melting form B.

"Question: You didn't perform any experiments regarding XRPD (sic) at Seres to identify a particular crystalline form of ibrutinib, correct?

"Answer: So we -- we did not have the capability of performing XRPD at Seres because we lacked the instrument.

"Question: Uh-hum.

"Answer: So I didn't run XRPD myself.

"Question: And you did not direct the XRPD testing that the third-party lab ran on the ibrutinib compound?

"Answer: I directed it because I sent samples to them and told them to run XRPD.

"Question: And did you direct them as to how to run the XRPD analysis that were run by the third-party lab?

"Answer: No.

"Question: If you could turn to column 63 of

the patent. If you see there in example 1, under example 1, it says preparation of crystalline forms and it has a compound.

"Do you see that?

"Answer: Yes.

"Question: And it's compound 1. That is -- is that ibrutinib?

"Answer: I believe it is, yes.

"Question: Okay. And under that there are listed three routes for Form A: Form A route 1, form A route 2, and Form A route 3.

"Do you see that?

"Answer: Yes.

"Question: You did not identify any forms other than form A or form B, according to your earlier testimony, during your work on the ibrutinib project, correct?

"Answer: So what I'm -- what I recall doing was focus -- the focus was on those two forms. I only really dealt from a manufacturing perspective with form A and form B. Those were the forms that were the most relevant to the manufacturing.

"So that's why they're in my memory as to the forms that we used at the time, that we had both of those relevant forms because we actually had made them.

"Question: And you don't remember identifying

or finding form C through F, correct?

"Answer: I do not.

"Question: What is the invention of the '753 patent?

"You're an inventor on the patent. I'm asking for what you believe the invention to be.

"Answer: The -- the invention is related to crystalline form.

"Question: What specifically about crystalline forms is the invention related to?

"Answer: So the patent identifies crystalline forms of ibrutinib.

"Question: I -- I'm just asking what you believe your invention to be.

"Answer: Crystalline forms of ibrutinib.

"Question: Okay. Anything else?

"Answer: As -- as directed in this patent? No. It's -- it's around the crystalline forms.

"Question: Fair to say that you did not contribute to the pharmaceutical formulation of ibrutinib?

"Answer: So my contribution was really to discover and produce ultimately when we manufactured crystalline forms of ibrutinib that are available to use in the pharmaceutical formulation. So from that aspect, yes, I contributed to the formulation.

"Question: Did you contribute to what was in the formulation?

"Answer: Only the active drug substance portion.

"Question: You have no experience in formulation generally, correct?

"Answer: I'm not trained in pharmaceutical formulations.

"Question: For example, you were not involved in the selection of what excipients to use in the ibrutinib capsule formulation, form; right?

"Answer: That's correct.

"Question: All right. When did you come up with the invention that is disclosed in the '753 patent?

"Answer: So the -- the research we did at Seres was mostly in 2007.

"Question: Is that it, just in 2007?

"Answer: Oh, no, it continued. I mean, we did certainly laboratory work in 2008, and then -- and we did manufacturing work again in 2009. So we -- we were doing work on that process throughout that.

"In -- in terms of specific experiments or when we did specific things, I would have to look at the laboratory notebooks to -- to try to identify, you know, a more specific date for a particular event.

"Question: What was Mark Smyth's contribution to the invention?

"Answer: So Mark -- Mark Smyth was the person at Pharmacyclics that I interacted with on a routine basis. And he and I discussed all aspects of the projects, including the solid state forms when we got to that point. So he was involved in the discussions.

"Question: He was involved in the discussions regarding what?

"Answer: All aspects of the project. So that would include the -- the crystalline forms that -- that we were working with and found, yes.

"Question: Okay. So what was his contribution to the invention?

"Answer: That I don't know.

"Question: Because it was that you discovered the crystalline form, correct?

"Answer: I believe I was the first person to run the experiments that I identified that -- that formed the crystalline forms. So I -- I first ran those experiments.

"Question: Okay. When was Erick Goldman's contribution to the invention of the '753 patent?

"Answer: I don't know that.

"Question: Okay. Norbert Purro, who is that?

"Answer: I do not know him.

"Question: And I -- I then assume you do not know what his contribution to this -- the invention of the '753 patent is?

"Answer: That's correct.

"Question: If you could pull out Exhibit -- I think it's Exhibit 5 now or -- 5 or 6 of the patent, '753 patent. Thank you.

"And if you look at column 66, line 20, there is a reference to the X-ray powdered diffraction for Form A, which is displayed in Figure 1.

"Do you see that?

"Answer: Yes.

"Question: And it mentions characteristic peaks, which include -- and then they refer to a number of peaks.

"Do you see that?

"Answer: Yes.

"Question: You were not involved in identifying those peaks as characteristic of form A with respect to your work on the ibrutinib project, correct?

"Answer: That's correct.

"Question: All right. And you did not actually identify these peaks as characteristic of form A as part of your responsibility or roles in the ibrutinib project,

correct?

"Answer: Correct.

"Question: Did you speak with Dr. Smyth after that e-mail exchange?

"Answer: About that subject?

"Question: Or just generally.

"Answer: I spoke to him, yes. I have spoken to him since, yes.

"Question: About what?

"Answer: About the Heroes of Chemistry Award.

"Question: And what is the Heroes of Chemistry Award?

"Answer: It's a national award given by the American Chemical Society for -- it's given to industrial chemists as -- as opposed to academic chemists for a particular project that was, I guess, deemed worthy of recognition.

"Question: And why were you talking to Dr. Smyth about the Heroes of Chemistry Award?

"Answer: So he contacted me to tell me that Pharmacyclics was planning to apply for it, and -- and that was some time before this. But this year it actually occurred. So the actual awards ceremony was in late August this past summer, and I attended in person. And Dr. Smyth was there. So I spoke with him at the -- at the

ceremony.

"Question: Okay. What were -- what were the award -- strike that.

"Were you nominated for an award?

"Answer: So the -- the -- the award goes to individual chemists, I think, so the chemists were listed by name and then it was related to a particular project.

"So, yes, I -- I was part of the team -- there were several -- that were associated with this project at Pharmacyclics, several chemists that were at the -- you know, simultaneously received this award.

"Question: Okay. And this was for the ibrutinib project that we're talking about?

"Answer: It was, yes.

"Question: Okay. Did you win the award?

"Answer: We did win, yes.

"Question: Would you -- and has it been routine in your practice that for any drugs that you're working with that exist in crystalline form, that you or someone else involved with the development of that drug would perform a polymorphic screen in order to control for that issue?

"Answer: In -- in the very early days of my career, no. But within the past 15 to 20 years, yes, it -- it has become common -- more commonly understood and brought to my attention having, again, worked on a couple at Lilly

many years ago. So I would now consider it part of the normal work that one would do to develop a pharmaceutical product.

"Question: And that's been the case throughout the last 15 to 20 years?

"Answer: Yes.

"Question: When you began working with ibrutinib, was there anything known about the crystallinity of batches of ibrutinib that had been prepared to that point?

"Answer: So my recollection is the first time that we discussed this with Mark Smyth, he indicated that they felt the material they had was amorphous.

"Question: When you first synthesized ibrutinib, was it using a process that was provided to you by PCYC?

"Answer: You're -- are you speaking about the entire synthetic sequence or -- or individual steps or --

"Question: To start with, I'm referring to the entire synthetic sequence.

"Answer: So the -- the sequence that they provided and the experimentals that they provided were the basis for the beginning of my research. So I don't remember, again, detailed experiments from that long ago without contacting the notebook pages. But I -- I would

have started with running experiments either the way that they ran them or in a very similar manner.

"Question: And what was the -- the purpose of your -- your work on ibrutinib in that time frame?

"Answer: So the -- in the initial beginning of the project, the -- the first challenge was around the process selection for the entire sequence.

"So began, of course, at the beginning where we had purchased starting materials and then began to work through sort of step at a time to see if this -- the first reaction would work and could it be performed well as was written, did it need modification and sort of would make an evaluation as you go along.

"So the -- the first step, and decide whether it needed improvements and what and how much and what the goals would be, and then moved on to the next step with a similar kind of evaluation and worked down the synthetic chain, really.

"Question: So effectively, you were tasked with refining the synthetic process for preparing ibrutinib?

"Answer: Yes.

"Question: During your efforts to refine the process, what is the first instance you recall with respect to the crystallinity of the finished ibrutinib product?

"When -- what was the first issue that came

about with respect to the crystallinity of that product?

"Answer: I don't recall there was an issue other than the fact that having known from Mark that they didn't have a crystalline form. I knew that when we got to that point, we didn't have a preset form to make.

"So we were -- I would have needed them to evaluate forms, look for forms or try to make forms, basically, because there was no -- there was no prior history of crystalline forms. So that was just the -- the work waiting to be done. And as I say, until we had some significant quantities.

"Question: Was it -- did you consider it preferable to have a crystalline form as opposed to an amorphous form of ibrutinib for the drug product?

"Answer: Yes.

"Question: Why is that?

"Answer: The -- in -- the advantage to the -- to a crystalline form in and in general in -- in a -- as a pharmaceutical product, not necessarily anything specific about ibrutinib, but the general reasons one would use a crystalline form would be to enhance stability. And that's both physical and chemical.

"So physical stability would relate to things like hygroscopicity. Typically amorphous materials are often more hygroscopic, and their water content varies as a

function of the relative humidity of their environment.

"And so that means that -- especially in some countries in the world where it's quite humid or some places where it's quite humid could be difficult to maintain a consistent form or potency of the material just because of the level of hydration going up and down.

"So physical stability would be one. Chemical stability is -- is another primary reason that traditionally in a lot of instances crystalline materials are just more stable chemically. Their rates of oxidation would be lower, for instance, reaction with -- with oxygen or with just thermal degradation. They tend to be faster in an amorphous or a glassy material than they do in a crystalline material.

"Question: Would you consider a polymorph of an API to be pure with respect to the API?

"Answer: In -- in my knowledge, purity has nothing to do with the form, per se.

"Question: But if I give you a polymorph of an API, would you -- strike that.

"If I give you a polymorph of an API, would you expect there to be any other chemical entity in the polymorph other than the API?

"Answer: So there's -- there's no such thing as a completely hundred percent pure compound anywhere in the

universe, to my knowledge.

"Question: Right.

"But I asked you about a polymorph, not a compound.

"Answer: So there is no substance that is a hundred percent pure polymorph or any other substance that is a hundred percent pure, just as a matter of scientific principle.

"Question: But you use recrystallization to remove impurities from your -- from your API, right?

"Answer: I have used recrystallization to improve the purity of a compound.

"Question: But in your experience, you're not able to completely remove impurities, right?

"Answer: Again, I would say when you say complete, that implies to me a hundred percent purity, meaning nothing else is possibly present. And that never is possible."

(End of videotaped deposition.)

MR. ABHYANKAR: Your Honor, a quick update. I understand that the missing exhibits have been sent to the Court and they are being printed.

THE COURT: I got them.

MR. ABHYANKAR: Sure.

THE COURT: All right. Ms. Bharkhda, anything?

You're on mute.

MS. BHARKHDA: I'm sorry. Who are we proceeding with next? I'm not sure I am clear on that.

MR. ABHYANKAR: If the Court has the printed out exhibits, then we can start. We might back up again unless the Court would like to start from the beginning.

THE COURT: No. Go ahead.

MS. BHARKHDA: I was going to say, as long as the Court has the exhibits that it needs, we've been rolling that out behind the scenes, that would be fine with us.

THE COURT: You might have to back up like three or four lines where we were.

MR. ABHYANKAR" okay.

THE COURT: With the introduction of Smyth 3.

MR. ABHYANKAR: Have you got it?

THE COURT: Hold on one second. All right.

MR. ABHYANKAR: Thank you, Your Honor.

(The videotaped deposition of Dr. Mark Smyth was played as follows.)

"Question: When you say the third-party manufacturer, you are referring to he was examining a recrystallization process, who specifically are you referring to?

"Answer: Dr. David Wirth.

"Question: Dr. David Wirth was from Seres?

"Answer: He worked at Seres, yes.

"Question: Was Dr. David Wirth your primary contact at Seres?

"Answer: Yes.

"Question: Who directed Dr. David Wirth to examine the recrystallization process at Seres?

"Answer: Me.

"Question: I am going to hand you what has been marked as Smyth Exhibit 3, a document bearing production numbers, and, Dr. Smyth, by production numbers, I am referring to these numbers that have been stamped at the bottom of each page on the right-hand side, which we call Bates numbers.

The production number IMBPCYC05002448 to IMBPCYC05002482.

"Dr. Smyth, do you recognize Exhibit 3?

"Answer: Yes.

"Question: If you turn over from the -- on the first page, it says No. 678; correct?

"On the first page it says No. 678; correct?

"Answer: It says that, yes.

"Question: If you turn it over, on the second page it says assigned to, and that is a handwritten name: Mark S. Smyth; is that right?

"Answer: Correct.

"Question: That's you; correct?

"Answer: Yes.

"Question: Does this lab notebook between the dates that we just went through -- 26 November of 2017 to April 27, 2010, -- does this time period reflected in the lab notebook accurately reflect the work that you personally performed in the lab BTK project?

"Answer: Yes. It reflects the time period.

"Question: I am just going to mark the patents all together.

"I'm handing you, Dr. Smyth, a document bearing production numbers IMBPCY04446283 to 352, which is U.S. patent No. 9,725,455.

"I am handing you a document which has been premarked as Smyth Exhibit 6, bearing production numbers IMBPCYC04446822 to 6892, which is U.S. Patent No. 10,106,548.

"I am marking as -- I am handing you, Dr. Smyth, what has been premarked as Smyth Exhibit 7, a document bearing production numbers IMBPCY04446893 to 6961, which is Patent No. 10,125,140.

"Dr. Smyth, looking at -- we can start with Exhibit 4, which is U.S. Patent No. 9,296,753 patent; correct?

"Answer: Yes.

"Question: For the purposes of this deposition, if I refer to this as '753 patent, you'll understand what I mean; correct?

"Answer: Yes.

"Question: Do you recognize this patent -- '753 patent?

"Answer: I don't recognize it by number.

"Question: Okay. If you turn over to the second page of the patent which has a production number, the last three digits end at 078.

"Do you see on the top upper right hand there is a line within parentheses that says 72, and it says inventors?

"Do you see that?

"Answer: Yes.

"Question: Your name is listed on the top, Mark Smyth; is that correct?

"Answer: Correct.

"Question: You are listed as an inventor on this '753 patent; correct?

"Answer: Correct.

"Question: How are you involved with this patent concerning -- that is titled crystalline forms of ibrutinib?

"Answer: I was responsible for leading all the

technical work on the project from both in-house efforts, as well as the third parties.

"Question: Okay. Your description of the contribution that you made to this patent, '753 -- your contribution was to lead the technical work on the project from in-house efforts, as well as third parties; is that correct?

"Answer: That was a significant part of it.

"The other part was to help make decisions on what to do next in the work.

"Question: I am just asking if you contributed to what has been described on this page on column 63 under form A, route 1.

"Answer: I can't recall specific contributions to what I would have done for this part or what I would have contributed for this particular excerpt.

"We did have discussions around which solvents to use in this aspect of the work; so I was involved in those discussions.

"Question: Do you recall where these solvents that are listed on route 1 from what we are looking at, column 63 under form A, route 1 -- where this list of solvents came from?

"Answer: They would have resulted from the discussions we had with everyone working on the project

about what to use to try and accomplish crystallizations based on the work that we had already performed with David Wirth or in-house efforts.

"Question: There was work performed on in-house efforts outside of David Wirth who was at Seres; correct?

"Answer: Correct.

"Question: Who performed those in-house efforts?

"Answer: Erick Goldman.

"Question: Okay. This is Dr. Erick Goldman, who is also listed as an inventor on the patent, '753; correct?

"Answer: Erick Goldman is listed as an inventor, yes.

"Question: Who is Erick Goldman?

"Answer: Erick Goldman is a scientist that I hired at Pharmacyclics to do process chemistry.

"Question: If you go back to your lab notebook, Exhibit 3.

"If you go to page 3 of your lab notebook, which has a production number ending in '458.

On the top of that page -- that page, on the left top is dated March 20, 2008; correct?

"Answer: Correct.

"Question: On the top of that page, the title

of this page that we are looking at -- that says generate acetone solvate of PCI-32765?

"Answer: I see that.

"Question: Do you recognize that as the registration code for ibrutinib that was used at Pharmacyclics?

"Answer: That is the internal code we used for the ibrutinib molecule. Yes.

"Question: By the efforts that you just mentioned, the in-house efforts that you mentioned, that you ran yourself, would that include what is reflected -- the in-house crystallization efforts that you ran yourself -- does this page reflect some of those efforts?

"Answer: Yes.

"Question: If you turn to page -- of your lab notebook page 10, which is -- the production number ends in 465.

"That page on the top left corner -- the date is October 17th, 2008; correct?

"Answer: Correct.

"Question: On the top of that page, the title is growth of X-ray quality crystals of PCI-32765, and within parentheses, it says lot 082032, and it says DMC/HEX.

"Do you see that?

"Answer: I see that.

"Question: Hex -- that would be hexane?

"Answer: Yes.

"Question: Does this page reflect some of the in-house crystallization efforts that you personally performed as part of the ibrutinib project that you just mentioned?

"Answer: This is a part of it. Yes.

"Question: Similarly, if you turn the page over to page 11, that is dated also October 17th, '08; correct?

"Answer: Yes.

"Question: That says on the top title X-ray crystals of 32765, EtOAc/Hex.

"Do you see that?

"Answer: I see that.

"Question: This would also reflect the part of the work that you did in-house on crystallization efforts of ibrutinib?

"Answer: Yes.

"Question: Similarly, the next page over, page 12, that's ending in production number 467.

"The start date is October 17th, 2008 on the top; correct?

"Answer: October 17th, yes.

"Question: That says X-ray crystals of 32765. Acetone/hex.

"Do you see that?

"Answer: I see that.

"Question: This page would reflect some of the in-house crystallization efforts that you performed on ibrutinib; correct?

"Answer: Correct.

"Question: Do you recall what SSCI is?

"Answer: That's the third-party lab that we had contracted through the work with Seres, as well as separately, to do some analysis of the solid state properties.

"Question: Were you involved in engaging SSCI for the work on ibrutinib?

"Answer: Yes.

"Question: When you say that SSCI, the third-party lab that was contracted the work at Seres, what do you mean by that?

"Answer: Initially, SSCI was used as an analysis lab, analytical lab by Seres. David Wirth had experience working with them before on other programs, and he recommended that we have samples sent through there with no other identifier other than a lab notebook number from him to get some data.

At a later date, we contracted SSCI separately. Question. I see. Thank you for that clarification.

At the time, initially, did Seres send any samples to SSCI by themselves for analysis?

"Answer: Not by themselves. It was always under my agreement or direction.

"Question: Other than those crystallization efforts that were intended for single crystal analysis, do you know if anyone at Pharmacyclics performed any crystallization efforts for powder diffraction analysis?

"Answer: During what period?

"Question: Before Dr. Goldman's work in 2010.

"Answer: Not that I can recall, no.

"Question: Do you know what Dr. Goldman's contribution was to this patent?

"Answer: As part of the project team, Erick had responsibilities for coordinating activities around solid state analysis once he joined the company. That was a part of his responsibilities.

"Question: You mentioned some in-house crystallization efforts that were conducted by Dr. Goldman; correct?

"Answer: He did a few experiments. Yes.

"Question: Okay. If you look at the -- again, the second page of your patent '753 and list of inventors,

also listed is Dr. David Wirth.

"Do you see that?

"Answer: Yes.

"Question: That's the same Dr. David Wirth that we were just talking about from Seres labs; is that right?

"Answer: Correct.

"Question: Do you know what Dr. Wirth's contribution was on the '753 patent?

"Answer: I can only comment on what his role in the project team was.

"Question: What was that?

"Answer: He was responsible for the experiments related to the process development activities and that led to the crystallization/recrystallization studies that led to the discovery of the polymorphs of ibrutinib.

"Question: Then other -- the fourth inventor listed on the '753 patent is Norbert Purro?

"Do you see that?

"Answer: I see that.

"Question: Do you know who Norbert Purro is?

"Answer: I know Norbert.

"Question: Who is Dr. Purro?

"Answer: Mr.

"Question: Mr. Purro?

"Answer: He is a scientist that worked on the pharmaceutical sciences portion of the project.

"Question: Do you know what Mr. Purro's contribution was to the '753 patent?

"Answer: I can only comment on what Norbert's role was in the project as a whole.

"Question: What was that?

"Answer: His role was to develop the formulation of the ibrutinib for clinical studies.

"Question: In terms of your role, your contribution with respect to the '753 patent, you were not involved in the formulation aspect; correct?

"Answer: No. As I already stated, I had nothing to do with the actual formulation work other than supplying API.

"Question: Okay. Going back to our discussion about your involvement on the polymorph analysis of ibrutinib at Pharmacyclics, when you mentioned that you were working through Dr. Wirth, you were working with SSCI at that time early after you had joined on the polymorph analysis of ibrutinib; correct?

"Answer: That's not entirely accurate. No.

"Question: Can you let me know what was inaccurate?

"Answer: David had, with our agreement and

direction, sent samples to SSCI when he first started doing the recrystallization work in early 2008 and encountered materials that looked and based differently than what we had seen before.

"He proposed it. We talked about it, and I agreed to have him send samples without any identifier other than a lab notebook number to SSCI.

"Later, in 2008, Pharmacyclics engaged SSCI directly to perform a solid state analysis.

"Question: Okay. Do you recall, other than SSCI, if any other third party performed polymorph analysis before SSCI did in early 2008 after you joined Pharmacyclics?

"Do you have that recollection?

"Answer: I don't recall anyone else doing any analysis of polymorphs prior to 2008.

"Question: Were you aware -- do you recall if anyone at Pharmacyclics had performed polymorph analysis on ibrutinib before you joined Pharmacyclics in November of 2007?

"Answer: I was not aware of anything that had been done.

"Question: Okay. Do you remember if anyone at Pharmacyclics had engaged a third party analysis lab to perform any polymorph analysis of ibrutinib prior to

joining -- you joining in November of 2007?

"Answer: I don't recall any activities in that area prior to my joining. No.

"Question: Okay. I am going to hand you, Dr. Smyth, what has been marked as Smyth Exhibit 10, which is an e-mail that has production number IMBPCY05289693, and then this e-mail has an attachment, which has been marked as Smyth Exhibit 11, and that has production numbers IMBPCYC05289694 to IMBPCYC05289712.

And what is the GMP lot?

"Answer: A good manufacturing practice. That is a designation associated with material prepared for dosing humans in clinical trials.

"Question: Would the GMP lot be associated with certain specifications?

"Answer: GMP lots are released according to accepted specifications.

"Question: How are those specifications set?

"Answer: In my personal experience, it is based or previous experience making that material and working in collaboration with the quality assurance, quality control, analytical chemistry, and the toxicology teams to define acceptable limits.

"Question: The GMP specification would be sent by -- the GMP specifications for ibrutinib would be sent

internally by Pharmacyclics personnel of these departments that you mentioned?

"Answer: They would have been involved in QC and analytical technology, quality assurance, and the manufacturing teams.

"Question: Would the GMP specification include a specification for crystal form?

"Answer: Not all GMP materials are intended for -- require a solid form analysis.

"Question: In your experience, what determines why a solid state specification is added to a GMP specification?

"Answer: In my experience, it has been added into a specification when control of a crystal form is desired for managing the properties of the solid.

"Question: In your experience, is a solid state specification for GMP included if there are issues encountered with crystal form -- with a crystal form?

"Answer: I don't know that I would characterize it as a problem on an issue. I believe I said it was used to help assure control and manage the solid state properties.

"Question: Now, after you engaged SSCI in doing the solid state analysis and polymorph analysis, do you recall reviewing reports from SSCI?

"Answer: Yes, as part of my job.

"Pharmacyclics engaged SSCI to conduct a polymorph screen about 2008; right?

"Answer: Correct.

"Question: Okay. Later on it -- you are aware of a polymorph screen that was conducted by a company called Pharmorphix; is that right?

"Answer: Yes.

"Question: Okay. What I'm handing you is a Smyth Deposition Exhibit 20. It has got Bates numbers IMBPCYC05275591 to 92.

"Do you have that in front of you?

"Answer: Yes.

"Question. Okay. And it is a letter. If you look at the back of the second page, it has your name and your signature on it; right?

"Answer: Yes.

"Question: Okay. The front page is dated March 9th, 2011, and it's to Paul Hirst. It says SAFC Pharmorphix.

"Do you see that?

"Answer: Yes.

"Question: Okay. If you look at the second page of the letter, at the top there's a sentence that discusses another potential polymorph has been observed.

"Do you see that?

"Answer: Yes.

"Question: Okay. It is referred to as unknown B material.

"Do you see that?

"Answer: I see the phrase unknown B material.

"Question: Okay. Do you know whether Pharmacyclics referred to that Unknown B material ultimately as polymorph form B of ibrutinib?

"Answer: I don't believe so. I believe that the DSC onset at 135 degrees -- that that polymorph was, I think, designated form C.

"Question: Okay. Are you -- how good is your recollection?

"Answer: As I said, I think. I am not 100 percent sure.

"Question: Did Pharmacyclics provide you with those proposed tests and studies for the polymorph study?

"Answer: As I stated about our work with SSCI, we always after a submission of request for proposal -- we would have a teleconference to discuss the project and start aligning on the tests, the solvents, anything else related to the project that we felt was needed to be discussed and agreed upon.

"Question: I've handed you what has been marked

Smyth Deposition Exhibit Number 24. It has Bates number IMBPCY05252966 to 037.

"Do you have that in front of you?

"Answer: I do.

"Question. Thierry Bonnaud? Do you see the name to the right?

"Answer: Yes.

"Question: Do you know who he is?

Answer. Thierry was one of the project leaders on most of the studies we conducted with Pharmorphix.

"Question: You interacted with him when it came to the polymorphism studies; correct?

"Answer: We had interactions with him, yes.

"Question: That one is dated February 28, 2012. That is actually a real date; right?

"Answer: Yes.

"Question: Do you recognize this as a report that Pharmorphix gave to Pharmacyclics detailing the polymorph study that Pharmorphix ran?

"Answer: This is a report on one of those studies that they conduct over the years. Yes.

"Question: Okay. Let me ask you again to go back to the patent.

"Do you have that?

When I say the patent, I mean Exhibit 4, the

'753 patent.

"Do you have that?

"Answer: I see Exhibit 4. Yes.

"Question: In the front, there's -- when I say the front, it is a few pages in. There's a Figure 1.

"Do you see that?

"Answer: I see Figure 1. Yes.

"Question: There's a number of figures after that, Figures 2 through 16.

"Do you see those?

"Answer: Yes.

"Question: Do you know who supplied the data that went into those figures?

"Answer: We gathered data from reports and submitted them to the patent agents. Erick and I did.

"Question: Do you know where the data came from?

"Answer: The data was -- not all of it. I expect that a majority of it came from the Pharmorphix work, if not all, but I don't know.

"(Exhibit 25 was marked for identification.)

"Question: What I'm handing you is Smyth deposition Exhibit Number 25, and it has Bates numbers IMBPCYC05316316 to 320.

"Do you have that in front of you?

"Okay. It is an e-mail chain, but I am focusing on the second e-mail on the front page from Thierry Bonnaud to Erick Goldman.

"Do you see that?

"Answer: Yes.

"Question: Dear Erick, find attached the data as requested for the patent.

"Do you see that?

"Answer: Yes.

"Question: That is from Pharmorphix; right?

"Answer: Yes.

"Question: That is consistent with what you thought, which is Pharmorphix supplied the data for the figures inside the patent?

"Answer: I didn't state that I believe they had submitted all of the data. I said they likely submitted most of it, if not all, but I don't know how much they submitted or when the data went into the actual application.

"Question: What I'm handing you is marked Smyth Deposition Exhibit 26, and it has Bates numbers IMBPCYC05316321 to 329.

"Do you have that in front of you?

"Answer: Yes.

"Question: If you go back to the previous exhibit, do you see that there's an attachment to the e-mail

at the top?

"Do you see underneath e-mail, it says attachments?

"Answer: Yes.

"Question: Do you see the document in front of you, the Exhibit 26?

"Answer: I see Exhibit 26, yes.

"Question: Okay. This is data that Pharmorphix would have supplied to you; correct?

"Answer: They would have supplied to Erick, and we would have -- we would have reviewed it together.

"Question: I am handing you a document marked as Smyth Exhibit 28.

"Is that an e-mail chain that you were part of on June 6th, 2008?

"Answer: It looks that way, yes.

"Question: I'd like to focus on the first e-mail in the chain.

Is that an e-mail from you to Dave Engers, Brett Cowant and Jing Teng?

"Answer: It looks that way, yes.

"Question: Those individuals were from SCSI; is that correct?

"Answer: SSCI.

"Question: Sorry. SSCI.

"Aptuit owned SSCI; is that correct?

"Answer: SSCI was an Aptuit company based on the e-signature of Brett Cowans, so, yes.

"Question: In your e-mail you refer to an IND for PCI-32765. Is that Investigational New Drug filing with the FDA?

"Answer: Yes.

"Question: You then state as such, we are working on the CMC sections which discuss crystal forms.

"Do you see that?

"Answer: Yes.

"Question: Why were you discussing crystal forms in the CMC section of the IND?

"Answer: I don't have an exact answer other than it was a section that we included since it was likely a specification of the material to control for crystal form.

"Question: Why was Pharmacyclics interested in controlling for the crystal form of ibrutinib?

"Answer: Because we found that there were multiple polymorphs during our development work, and we wanted to make sure we controlled for the most stable form.

"Question: Why did Pharmacyclics want to have the most stable crystalline form for ibrutinib in its drug product?

"Answer: I didn't say anything about drug

product. I only worked on the API. The goal was to have the most physically and chemically stable form, and that's what our goal was.

"Question: Obviously, you were going to use it in a drug product for trials; right?

"Answer: It was going into drug product for trials. Yes.

"Question: That's why you file an IND -- is to do a trial; is that correct?

"Answer: You file an IND to get into clinical trials, yes.

"Question: Why was Pharmacyclics interested in including the most stable crystalline form of ibrutinib in the product used in its clinical trials?

"Answer: We wanted the most stable crystal form possible, both chemically and physically, so that there was no degradation in storage.

"Question: Would you agree that the desire to have an active drug ingredient that has good stability during storage is generally considered desirable to drug developers in that time frame?

"Answer: In my experience, that is a common goal of projects I've worked on.

"Question: Do you know when in time you came to call a particular form as form A?

"Answer: It was, I believe, after the SSCI work was done that we had contracted with them.

"Question: Why did you ascribe whatever form you ascribed form A to that name?

"Answer: I believe that came out of their internal nomenclature for a sample. I don't know where that originated other than that.

"Question: In 2008, Pharmacyclics had SSCI perform that polymorphic screen; correct?

"Answer: That was in 2008, yes.

"Question: During that time, they identified what they called form A; is that correct?

"Answer: They labeled something it was identified, yes, later as form A. They're the ones who gave that designation.

"Question: The Pharmorphix polymorph screening was intended to be a more robust polymorphic screen relative to the SSCI screen; is that correct?

"Answer: Our intention was to do a more thorough study, yes.

"Question: You are in Exhibit 24?

"Answer: I have that in front of me.

"Question: It is hard when you are coordinating with different -- okay. That's why.

"Let's turn to page 972.

"Answer: In Exhibit 24?

"Question: Yes.

If you could turn to the last paragraph on page 972, it states the polymorphic screen -- paren -- including cooling, maturation, anti-solvent, addition, and slow evaporation -- end paren -- consistently yielded form A, other than one sample which gave an XRPD diffractogram pattern differing slightly to form A -- period. This converted to form A readily at ambient temperature so was not fully studied.

"Do you see that?

"Answer: I see that.

"Question: Is it consistent with your recollection that the screening of ibrutinib performed by Pharmorphix consistently yielded form A?

"Answer: I gathered that from reading this paragraph. Yes.

"Question: If we could turn to the next page.

In the second paragraph, second sentence, it states form A was shown to be prepared easily and readily at elevated temperatures -- paren -- above 25 degrees Celsius and almost in all cases at 50 degrees Celsius end paren -- however, the other forms -- paren -- B and C and newly identified mono-MIB K solvate -- end paren -- were isolated when the slurries were exposed to sub-ambient temperatures.

"Do you see that?

"Answer: Yes.

"Question: Do you agree that form A was prepared easily and readily?

"Answer: Based on what they state here, yes.

"Question: Is that consistent with your experience in working with crystalline forms of ibrutinib?

"Answer: Form A tended to be the predominant form that was generated. Yes.

"Question: In the next paragraph, they say that form A was easily prepared from numerous solvents.

"Do you see that?

"Answer: Yes.

"Question: Is that also consistent with your experience in dealing with crystalline forms of ibrutinib in varying solvents?

"Answer: Based on the study and the report here, yes. It says that.

"Question: Is that also consistent with your experience and recollection of polymorphic screening of form A for executing of ibrutinib?

"Answer: Form A was always the predominant form that we saw, so, yes.

"Question: Was the purpose of this study to try and get as many -- identify as many polymorphic forms of

ibrutinib as they could?

"Answer: That was a stated purpose, yes.

"Question: To do that, they used an amorphous form of ibrutinib at the beginning of the studies; correct?

"Answer: Correct.

"Question: With that same goal of identifying new and different polymorphic forms of ibrutinib, they also used multiple solvents under various conditions; is that correct?

"Answer: Yes.

"Question: Do you know if there's any other reason to use an amorphous state of the drug as a starting point for polymorphic screens beyond improving the likelihood that you get a variety of forms?

"Answer: I recall the discussions around making sure that the amorphous form was used to reduce the chance of crystalline forms acting as seeds in these studies.

"Question: Would a crystalline form, acting as a seed, tend to end up with that finished product from the test being the same thing you started with?

"Answer: Seed would likely result in that form being generated.

"Question: If the sample fully dissolved, would that still be a concern?

"Answer: You would have to determine how

completely dissolved it was to have confidence that there's nothing left behind.

"Question: If you could jump down to page 011, the conclusions section of the report, in the first paragraph in the second sentence, they state, form A was the most readily prepared crystalline form, prepared from numerous solvents using various techniques; is that correct?

"Answer: It reads as such.

"Question: You agree with that statement; correct?

"Answer: I recall from the work that I've just reviewed in here and seen and what I remember is, yes, that was accurate.

"Question: The next paragraph they indicate in the last sentence the ease to controllable produce form A was also a significant advantage over forms B and C, which were difficult to reproduce confidently and would risk conversion to the more stable form A; is that correct?

"Answer: That's what it reads.

"Question: Do you agree with that sentence?

"Answer: From what I remember of this study, that was correct.

"Question: In the last paragraph they state form A was proven to be the most easily prepared with control when using the appropriate solvents and was stable

with the highest melting temperature of all the forms identified; therefore, form A was recommended as the ideal crystalline form to progress with in development, in the solvents and conditions previously stated.

"Do you see that?

"Answer: I see that.

"Question: Do you agree with that conclusion?

"Answer: Yes.

"Question: Do you recall forms B and C converting to form A during storage or during the experiments that were performed involving forms B and C?

"Answer: I'd have to review the data. I think there may have been some conversion studies that saw that occurring.

"Question: Do you recall any issues of form A converting to a different form?

"Answer: Not that I recall.

"Question: Outside of that, do you recall you, David Wirth, or Mr. Goldman ever trying to identify peaks that differentiated between the different forms of ibrutinib that you had identified?

"Answer: As a practice, we did not focus on single peaks as identifiers alone.

"Question: How about two or three peaks?

"Answer: It was our -- my practice for sure to

use as many peaks as possible in a comparison to a known standard to identify whether a sample was a certain form or not.

"Question: Okay. For the record, Dr. Smyth is looking at Exhibit 5, the '455 patent.

If we could turn to column 3, in the paragraph beginning at about line 10 -- 9 or 10 in the second sentence -- in that paragraph there's a reference to characteristic peaks of form A.

"Do you know who identified those peaks as being characteristic of form A?

"Answer: I don't know what individual would have called those as such.

"Question: Do you think it was any of you, David Wirth, or Mr. Goldman?

"Answer: As I said, I don't know who actually identified those as characteristic.

"Question: Did you have any involvement with forms D through F?

"Answer: I was involved in the technical team interacting with the third party that labeled those as D, E and F at the time.

"Question: You are referring to form A when you refer to the free base polymorphic form; right?

"Answer: That is the form that we went forward

with in the clinical studies.

"Question: All right.

Dr. Smyth, I've just handed you Smyth Exhibit 37. It is labeled Bates IMBPCYC05622162.

"Do you have the document in front of you?

"Answer: Yes.

"Question. Have you seen this document before?

"Answer: It looks somewhat familiar. Yes.

"Question: Is it an internal Pharmacyclics report; correct?

"Answer: It is an internal of document, yes.

"Question: Okay. It reads micronized ibrutinib form A is the active ingredient in ibrutinib capsule, 140 milligram, which is in clinical development at Pharmacyclics.

"Do you see that?

"Answer: Yes.

"Question: Do you agree with that statement?

"Answer: At the time it appears to have been accurate, yes.

"Question: We looked at Exhibit 17 before.

"My understanding from your explanation was that this was a proposed research protocol from SSCI that you placed comments on.

"Do you recall that?

"Answer: Yes.

"Question: Let me ask you to turn to the Bates numbered, labeled page ending in 621.

"Answer: Okay.

"Question: Now, under goal one, where it says perform analytical characterization of material as received -- do you see that?

"Answer: Yes.

"Question: The proposal that you received from SSCI did not include XRPD or DSC as a proposed analytical technique; is that right?

"Answer: Not at that stage, no.

"Question. You added them here on the side?

"Answer: Yes. That's my handwriting.

"Question: Okay. Ultimately, those experiments were performed; is that correct?

"Answer: Yes.

"Question: You added those to the experimental protocol for the studies that you engaged SSCI to do in the spring of 2008?

"Answer: From that part of the study, yes, I added those analytical techniques.

"Question: Finally, let me have you look at Exhibit 16.

"Answer: Okay.

"Question: If you -- Exhibit 16 was the work order from SSCI -- excuse me -- for SSCI that we were looking at earlier; is that right?

"Answer: As I recall, this was the work order that resulted in that proposal.

"Question: Okay. Let me turn you to the page ending in Bates number 20 -- 020. Excuse me.

"Answer: Okay.

"Question: Under changes, do you see the paragraph that says, since this protocol is research based, minor changes in the experimental approach or scope can be made based on scientific judgment?

"Do you see that?

"Answer: Yes.

"Question: Such changes can be agreed to by SSCI and Pharmacyclics' scientific contact person via telephone, facsimile, or e-mail discussions, which will be recorded at SSCI in the form of contacted reports.

"Do you see that?

"Answer: Yes.

"Question: SSCI I could not make minor changes to the experimental approach without your approval; correct?

"Answer: Correct."

(End of videotaped deposition.)

THE COURT: Okay. Thank you.

All right. What's next? Thank you. All right. What's next?

MR. ABHYANKAR: Thanks, Judge Connolly. We're now done with the deposition clips for the polymorph patents. We are going to move to a different technology area now.

THE COURT: Okay.

MR. ABHYANKAR: And Sandoz intends to call Dr. Maureen Donovan. We're going to talk about the pharmaceutical formulation patent and specifically the '231, which is asserted against Sandoz.

If I may suggest, I believe it is 10:40. If this is a good time for a break, we can break and then start up or we can proceed.

THE COURT: What I'm going to do is, we're going to take a 15-minute break, but what I would like is, I would like counsel from both sides to give me a five-minute summary of why what I've heard is significant to the case? All right.

MR. ABHYANKAR: Thank you.

THE COURT: We'll be back at 5 of 11:00 Eastern time. Thanks.

MR. ABHYANKAR: Understood. Thank you.

(Short recess taken.)

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(Proceedings resumed after the short recess.)

THE COURT: All right. Are you all there, I think? Can you hear me?

All right. Ms. Clayton, tell me very, very briefly. What is the significance of what I've heard this morning?

MS. CLAYTON: What you've heard this morning is from two of the inventors on the '548 patent, Your Honor, a Dr. Smyth and a Dr. Wirth.

We believe that that testimony is relevant to two different issues in this case. The first is related to the 112 issue -- actually, three issues. 112 issue on written description. We believe that the testimony shows that plaintiffs conducted extensive polymorph testing in advance of filing what eventually became the '548 patent which has a priority date of June 4, 2012, and that despite that significant testing, they only discovered and had identified forms A through F. So the only forms they actually were in possession of was those forms as of that date.

Secondly, Your Honor, there was some testimony related to enablement from I believe Dr. Smyth, related to some seeding experiment testimony, and maybe a couple of other nuggets in there that I'm forgetting. So there were maybe a handful of comments that were relevant to enablement

and obtaining new crystalline forms.

And then, third, we believe that that testimony shows that for forms A through C of ibrutinib, the characterization and thus the peaks that are recited in the '548 patent were not discovered by either Dr. Smyth or Mr. Wirth. Instead, they were done by a company called SSCI, and so unknown employees from SSCI should be named as inventors on the patent.

And then, additionally, for forms D and F, which plaintiffs belatedly in Dr. Myerson's expert report noted for the first time they thought came within certain of the claims.

THE COURT: Hold up. See, sorry. Go back. Avoid the clauses. Just get to the right point.

MS. CLAYTON: Yes. So --

THE COURT: You distracted me. I had it and I went off. So what's the point?

MS. CLAYTON: Yes. So for Pharmorphix, another third party invented and identified forms D and E and so they should also be named as inventors on the '548 patent and they are not.

THE COURT: Okay. Your first point is a 112 point.

MS. CLAYTON: Correct.

THE COURT: And 112 with a couple clauses.

What's the first 112 point?

MS. CLAYTON: 112, written description.

THE COURT: Right.

MS. CLAYTON: This testimony shows the only forms they were in possession of, which is the standard for written description as of June 4th, 2012, were forms A through F.

THE COURT: Okay.

MS. CLAYTON: A through F. Yes, Your Honor.

THE COURT: Your second 112?

MS. CLAYTON: Our second point on enablement, Your Honor, there are just some admissions in these and, frankly, Your Honor, I apologize. I can't remember them off the top of my head.

THE COURT: That's okay.

MS. CLAYTON: That go to establishing some of the factors related to undue experimentation and showing that there would be undue experimentation required.

THE COURT: That makes sense. Okay. All right.

Mr. Gutman, do you have anything to add to that?

MR. GUTMAN: Yes, I do, Your Honor. So yesterday you heard testimony from Dr. Swift that the claims of the '455 crystalline form patents are obvious in view of the prior art, including the '444 patent.

The testimony that you heard today from doctors

Smyth and Wirth, who are both named inventors on the '444 patent, are consistent with and further support Dr. Swift's opinions that the claims of the '455 patent are invalid for obviousness.

More particularly, you heard testimony from Drs. Smyth and Wirth that consistent with Dr. Swift's testimony, that a person of ordinary skill in the art would have been motivated to do a polymorph screen, especially for pharmaceutical products in order to obtain and identify the most stable crystal form.

You also heard testimony from Drs. Smyth and Wirth that the most stable crystalline form was form A and that it was easily and consistently obtained, and that even when they obtained other crystalline forms, such as forms B and C, those converted to form A.

So the argument is in total, that testimony supports the analysis conducted by Dr. Swift with respect to obviousness, that one of ordinary skill in the art would have been motivated to obtain form A, and they would have had a reasonable expectation of success at obtaining form A.

THE COURT: Okay. Thank you. All right. Mr. Sipes?

MR. SIPES: Your Honor, we disagree on the significance.

THE COURT: Go ahead.

MR. SIPES: To begin, we do agree on one thing. This is the testimony of the inventors and that's very important because the law is quite clear that, in fact, the path that the inventors took to the invention is never a proper analysis for obviousness. That's just basic law and it make makes a lot of sense. Otherwise, nothing would be obvious.

What it is relevant to, we believe, is understanding what they did and what they thought they were putting into their patent application, and in particular, you heard testimony, one, I think, that they developed a very robust path for the production of particularly crystalline form A, which I think, I tend to agree, does tend to show understand enablement that the patents clearly enable the production of A, but also that they worked with their form that they developed.

Once they had achieved crystalline forms -- you heard a reference, for example, for seeding and whatnot, that once they had a crystalline form. Remember, the time frame is very important. Before you have any crystalline material and after once you've developed the crystalline material, they worked with the crystalline material to then develop new crystalline forms, and that is what was in the literature, too. So it shows, and that they described that.

But candidly, for purposes of 103, the proper analysis is to look at the prior art, not what the inventors say. And even for 112 issues such as enablement and written description, I must disagree with Ms. Clayton. It would be nice if we could do a written description invention by peering into the heads of inventors and just examining what's in their mind. That's not the law. The law is you read the patent specification and you understand what it communicates to a person of ordinary skill in the art.

So we're not going so far to say because they said that they really thought of themselves as the inventor of crystalline ibrutinib, that is there was no crystalline ibrutinib until they made it. That's not the test. The test is what the patent application describes.

We do think it's significant that as they recognized, they were the first to crystallize ibrutinib, but we recognize the focus is on on the application. It's important that they were the inventors of crystalline ibrutinib, but we need to look at the application.

The reference to these contract laboratories we think candidly, Your Honor, is a distraction. It is, of course, true that as a small company, Pharmacyclics did contact with other companies to assist with the work, but the question here for invention versus conception and is everyone is agreeing, we're hearing from the inventors on

that.

So we actually think, A, the direction, and, B, it's not really a theory that is properly in the case, but we don't need to address that now. But we don't deny the fact that they worked with contract labs in developing crystalline forms.

THE COURT: Let me follow up on that idea of conception. Okay. So I take it, I mean, it's undisputed that under patent law, you can patent the genus of a molecule. Right?

MR. SIPES: That's correct, Your Honor.

THE COURT: Right. Ms. Clayton, you agree with that?

MS. CLAYTON: I agree with that, Your Honor.

THE COURT: Mr. Gutman, you agree with that?

MR. GUTMAN: If you have appropriate support. Yes, Your Honor.

THE COURT: All right. So, now, the conception that a molecule could be embodied in a crystalline form, right?

Are you saying, Mr. Sipes, that just having the idea, the conception that a particular drug molecule could have a crystalline form, that that is an invention?

MR. SIPES: Not, not alone conceding that it could be crystalline. I'm saying if you have an

invention --

THE COURT: Sorry. Let me step back. I'm asking in the abstract. I'm not asking about this particular thing. I just want to make sure. Is it your position that, you know, you've got a molecule and everybody agrees, you can patent a molecule.

MR. SIPES: Right.

THE COURT: Let's say the molecule was already patented, but then somebody said, hey, I just thought about this. I think that this molecule can take a crystalline form.

Are you telling me that conception is patentable?

MR. SIPES: Yes. If it is the case that the molecule has been made but only amorphously, so that, in fact, achieving a crystalline form is an accomplishment and if it proves that the crystalline form has useful properties, the invention has to be useful so that you, in essence, came up with the first crystalline form of a material that had useful properties, yes.

THE COURT: You get the patent?

MR. SIPES: You are entitled to a patent on crystalline material.

THE COURT: So hold on.

MR. SIPES: The opening --

THE COURT: Hold on. I'm sorry. Look, you're all very good, you know. I'm only cutting to the chase because I'm not -- it takes me awhile to get things. I think that's pretty clear and I'm sorry about that, but a lot to master for me.

I want to cut to where I'm thinking, if you don't mind, because I think it has taken me probably a lot longer than it took you all to figure out the nub of the dispute, at least some of them here.

Let's posit again. I've got a molecule and it has been patented and it's in amorphous form, but then I came up. I'm like, wait, wait a second. I can crystallize this. And I think, as I understand it, the plaintiffs' position is, hey, if I'm the one who comes up with the first crystalline form and I get a patent for -- I can get a patent at that stage for all crystalline forms of that molecule, that is your position. Right?

MR. SIPES: Yes, that is our position, but there's an important point here. Not only did you conceive of the crystalline form and make the crystalline form, but you recognized its useful properties.

THE COURT: You know, I'm getting -- I'm giving you that. That's fine. We'll just posit that. Okay?

MR. SIPES: Yes.

THE COURT: I don't think that's the nub of the

dispute, frankly. I think the defendants will agree with you. You've got to have usefulness. Right, Ms. Clayton?

MS. CLAYTON: Yes. I agree.

THE COURT: That is a distraction, frankly, I think. I want to focus on what I think I have to decide.

MR. SIPES: Yes.

THE COURT: And I think whereas the defense is saying, hey, you know what, if you come up with a specific crystalline form of a patent, you get to get a patent on that, but you don't get it for any and all crystalline forms. Is that correct?

MS. CLAYTON: That's correct, Your Honor. They should only be entitled to a patent on the exact crystalline forms they had discovered as of the filing date.

THE COURT: Mr. Gutman, you agree with that?

MR. GUTMAN: Not if the prior art says that --

THE COURT: That's not the question. This is an abstract. This is a hypothetical. I'm going to then, frankly -- I think I know where the law is on that.

Okay. So, of course, Mr. Gutman, I'm positing that it's not obvious. This is a discussion to get to the heart of the matter.

MR. GUTMAN: Yes, Your Honor. Theoretically, I agree with that.

THE COURT: Okay. Thanks.

MR. SIPES: Your Honor, here's an analogy that may help a little bit and if not, I apologize, but I think it's helpful.

Let's go back to the original invention of ibrutinib or any drug molecule. It's uncontested when they made it, it came out amorphous, but what they found is it's a useful molecule. And the claim covers that useful molecule even if it's used in forms beyond what they found. For example, crystalline form of the molecule.

THE COURT: When you said useful molecule, the molecule can exist in amorphous or polymorphous form. Right?

MR. SIPES: Correct.

THE COURT: There was at some point a patent for ibrutinib that did not limit it to amorphous or polymorphous. Is that correct?

MR. SIPES: That's the patent at issue in this case. Claim 10 of the '309 patent claims ibrutinib regardless of form. You can think of it in one sense as a genus patent. That molecule, ibrutinib, in any physical form. It would cover ibrutinib gas. It would cover ibrutinib liquid.

THE COURT: Wait. But I thought -- the way I broke this down in my own brain was, no, the '309 is broader. '309 is the compound.

MR. SIPES: Correct.

THE COURT: The '548 patent -- and I am focusing right now, at least in my brain, and I'm going to guess Ms. Clayton agrees with the way I'm focusing. I was focusing on the '548 patent, the crystalline form patent.

MR. SIPES: Correct, Your Honor. I'm trying to make an analogy, and maybe it was a bad one. You understand the '309 patent to cover ibrutinib molecules in any physical form.

THE COURT: Again, see, I don't think their defense is going to dispute that.

MR. SIPES: Correct.

THE COURT: Hold on, because if you think they are, but I didn't think they were.

MR. SIPES: I don't think so either, Your Honor.

THE COURT: Okay. Well, then, we're good, but I'm focusing on the '548 patent.

I think what's going on if I really want to cut to the heart of the dispute is that you want to say, Mr. Sipes, that you can not only patent the molecule as a genus, but you get the patent as a genus, all crystalline forms of the molecule. That's what you are saying. Right?

MR. SIPES: I would say that's a possible claim. This claim here is more limited than that, but, yes. I'm saying you're the inventor of crystalline ibrutinib, you get

all forms.

THE COURT: You get all forms even if you only disclose in the written description six forms. You're saying you get all forms if the claim says a crystalline form. Right?

MR. SIPES: Right. There are examples that we'll put in the record that show that the art recognizes that. That as the inventor of a crystalline material, you're entitled to claim a crystalline material.

THE COURT: So here's what I want to understand. So is there case law, you know? I mean, for instance, let's me ask you this: When did the idea of crystalline form, when was -- does anybody know when the first crystalline form was patented?

MR. GUTMAN: It was decades ago, Your Honor, decades. And you only really, I think, you know, as far as pharmaceutical products have existed because there has been a motivation to search for crystalline forms. You heard the inventors themselves say that people were doing polymorphic screens, you know, over the last 20 years, so --

THE COURT: Right.

MR. GUTMAN: It has been decades.

THE COURT: I'm just curious when you say decades. I didn't get the impression it has been 50 years. I got the impression it might be more like 25 years when

somebody maybe first started actually patenting crystalline forms of a molecule. You think it's 50 years? Okay.

I've got -- has the Federal Circuit dealt with this issue of whether you can patent specific crystalline forms versus any and all crystalline forms? Is there a case that addresses that issue?

MR. SIPES: The leading case, Your Honor, is the Gruenthal case, which we've talked about, but that was a different issue. That was really the nonobviousness of making the first crystalline form.

I'd have to -- I'm not aware of a Federal Circuit case specifically on a genus of crystalline forms. There are other Federal Circuit cases on genuses of other things, like antibodies.

THE COURT: Right. I get that.

MR. SIPES: But this seems -- well, it's true that crystals themselves are old. In fact, we're enmeshed in it now. The idea of different crystalline forms and polymorphs is actually relatively recent.

THE COURT: That's what I thought. In fact, you know, I read somewhere, and, you know, I'm not going to base my ruling on it unless one of you brought it up. I've read actually it wasn't until the HIV drug that somebody realized that the drug product could exist in various crystalline forms.

Am I way off on that?

MR. SIPES: I believe it's Ritonavir.

THE COURT: Exactly. I think it's in the mid '90s, isn't it? It's the mid nine tease?

MR. SIPES: Correct. And I wouldn't say that people didn't know before then that you had different crystalline forms, but that emphasized the importance of developing a first form that was stable.

THE COURT: Right.

MR. SIPES: That's when polymorphic stability in the pharmaceutical art became a real focus and ibrutinib talked about this.

THE COURT: Okay. So --

MR. SIPES: The achievement of the first stable form.

THE COURT: You said Gruenthal you were talking about. Was that in your opening?

MR. SIPES: It's in our opening slides. I apologize.

THE COURT: You don't have to apologize. That's the problem. I can only digest so much. I think what I'm digesting now is -- obvious is a very bad word.

Let me go back and ask the others. Mr. Gutman, Ms. Clayton, is there a Federal Circuit case that you would recommend that I read that addresses either directly or

indirectly this idea of can you patent any and all crystalline forms versus specific crystalline forms only? I will let Ms. Clayton go first.

MS. CLAYTON: So, Your Honor, we have looked. There is not a single Federal Circuit case that talks about crystalline forms as a genus, and we actually think that that demonstrates why this concept makes no sense in the crystalline art.

Now, there are cases where we can draw analogies even in the antibody context. For example, there's a case, AbbVie v. Janssen, which is ironic, those are the two plaintiffs in this case, that we think is very instructive in terms of why there is lack of written description here. Again, it's not exactly in this art. Basically, we do think it's instructive to the Court in terms of how the written description analysis should be conducted here.

THE COURT: Okay. Mr. Gutman, any case that you would point to me?

MR. GUTMAN: None that says as a matter of law, someone is entitled to a genus.

THE COURT: Okay.

MR. GUTMAN: Of a crystalline form. I think it's a sense of inquiry. I think it just depends on the facts.

THE COURT: All right. Now, the other thing

was, I was kind of recalling back to one of the Markman hearings. The problem is there were multiple ones in this case. And was there an '889 patent involved in the case at one point?

MS. CLAYTON: Not in the Sandoz case, Your Honor.

MS. ANDERSEN: Yes, Your Honor, but it has been quite a while since that patent was involved in the case.

THE COURT: All right. Well, I don't know if it was the '889 patent, and I thought this was Sandoz, not Alvogen. But I thought at some point, one of the defendants wanted me to limit my construction of crystalline form to crystalline form A.

MS. CLAYTON: The defendants collectively previously asked to limit to form A because the two peaks that are recited in those claims are only listed as characteristic for form A.

Your Honor said that because it talked about other embodiments, namely, A through F, you didn't think that that limitation was appropriate.

THE COURT: Right. I didn't think it was clear and unequivocal and I still don't. What I want to ask you: If I had adopted your construction, that we would not be in -- you would not have a 112 argument. Is that right?

MS. CLAYTON: Correct, Your Honor. That's

correct.

THE COURT: All right. I'm just curious. You think that's the better construction? I should have construed the patent to limit it to form A than deal with this invalidity issue? That would take the invalidity issue off the table. Right?

MS. CLAYTON: So I do believe that form A is the correct construction because the only form that has those two characteristics identified in the specification is form A.

Plaintiffs have pointed to little blips on the patterns to say that other forms, namely, forms D, F and C also have some of those peaks. We didn't think that that was an issue really worth disputing here, so I do think the better construction is A, but certainly, it shouldn't be broader than A through F.

THE COURT: And I'm just wondering, the plaintiffs, you have not changed your position, have you, during the course of this trial? Maybe we would be better off construing the patent as limited to form A.

MR. SIPES: No. And, in fact, Your Honor, we think this is an important issue and it's an important issue in this case and, candidly, I think, ultimately, it's an important issue for the pharmaceutical industry.

THE COURT: That's my sense. Always my

instincts are not to have to decide something I don't have to decide. Okay.

MR. SIPES: Your Honor, I wish I could make the case earlier. Unfortunately, it turns out to be a very important case.

THE COURT: No. That's all right. Okay. Well, look, that was very helpful to me. Again, my apologies. You know, there's a lot of good advocacy, but sometimes it's just too much to digest. And I harken back to your openings. I'm sure you gave me tons of stuff that is only now becoming apparent to me, the significance of it.

So all right. Where do we go next?

MR. SIPES: Thank you, Your Honor.

MS. CLAYTON: Your Honor, at this time Sandoz would call Dr. Maureen Donovan to the stand. And Mr. Abhyankar will be conducting that examination.

THE COURT: All right. Thank you.

... DR. MAUREEN DONOVAN, having been duly affirmed as a witness, was examined and testified as follows ...

THE COURT: Go ahead, counsel.

MR. ABHYANKAR: Thank you, Your Honor.

BY MR. ABHYANKAR:

Q. Good morning, Dr. Donovan.

A. Good morning.

Q. **By whom are you employed?**

A. **The University of Iowa.**

Q. **And what is your current position at the University of Iowa?**

A. **I'm currently Professor of Pharmacy.**

Q. **And before we discuss your opinions, I'd like to talk a little bit about your background. Could you please put up DTX-2391.**

Dr. Donovan, what is this document?

A. **This is a copy of my C.V. submitted in this case.**

Q. **Does this accurately reflect your academic and professional history?**

A. **Yes, it does.**

Q. **Great. And have you prepared demonstratives that will assist with your testimony today?**

A. **Yes, I have.**

Q. **Can we pull up slide 2? Dr. Donovan, can you briefly give us the highlights of your education?**

A. **Sure. I completed my Bachelor's degree in Pharmacy from the University of Minnesota. I went on to my graduate studies at the University of Michigan and completed a Ph.D. in pharmaceutics and then went on to my first academic position at the University of Iowa.**

Q. **Great?**

THE COURT: Dr. Donovan, sorry to interrupt.

Have you testified in my courtroom before?

THE WITNESS: To be honest, I can't remember. I don't -- I don't think I have.

THE COURT: Okay. All right. Thanks. Sorry to interrupt.

MR. ABHYANKAR: No problem.

BY MR. ABHYANKAR:

Q. **So what academic positions have you held at the University of Iowa up you until now?**

A. **I started as an assistants professor. I worked my way up the ranks to professor and that's the title I currently hold. And during the time that I've been at the University of Iowa, I've had several administration -- administrative positions also.**

So for a period of time I was division head of the Division of Pharmaceutics and Translational Therapeutics. I most recently served as the associate dean for undergraduate education in College Pharm.

Q. **In your work as a professor, have you had a particular area of research that you've been more interested in than others?**

A. **Yes. So my research interests all the way from actually undergraduate studies is in the mechanisms of drug absorption, and as a pharmaceutical scientist, I joined my interest in material sciences and formulation with that**

interest in drug absorption to defining and determining ways of optimizing formulations to improve or control drug absorption.

Q. **And is one of those research areas in the internasal field?**

A. **Yes. My Ph.D. dissertation was on an effective nasal absorption, and I've continued to do research in the area of nasal formulation, nasal absorption. And I do that -- in many ways I look at a number of delivery sites, routes of administration, each of them different. Each of them have particular characteristics that make them interesting and useful and sometimes compare the positive or negative aspects of a particular site to any other site. In particular, most commonly delivered sites like the gastrointestinal tract or like IV therapy.**

Q. **And when you say delivery sites like the gastrointestinal tract, are you referring to oral pharmaceutical formulations or drugs?**

A. **Yes. So anything -- anything that gets to the gastrointestinal tract, typically, that's through the mouth. But gastrointestinal tract involves the stomach and intestines. Oral delivery is actually broader than that because it involves the oral cavity, too.**

Q. **But that has been a part of your research since you start at the University of Iowa?**

A. **Yes, it has. I mean, again, I typically compare -- if I'm working in nasal delivery or topical, oftentimes I'm going to be comparing my results to the absorption characteristics of a similar compound, gastrointestinally or or transporters or cells, what we're look at.**

Just compare gastrointestinal absorption in many cases, not all, because it's not relevant in all. But as a comparator site, there's a lot of information that gastrointestinal absorption in particular, so it makes it a prime candidate for comparison.

Q. **Throughout the course of your career, have you presented at lectures and seminars related to pharmaceutical formulations?**

A. **Sure. I've given invited presentations at international national meetings and national meetings and academic institutions, both internationally and in the United States, in the pharmaceutical industry numbers of times, so, yes, I've given a number of presentations.**

Q. **What about published articles in peer-reviewed journals? Have you published any papers related to pharmaceutical formulation?**

A. **Yes, I've published over 50 papers that are related to drug absorption or pharmaceutical formulation. I have over 100 published abstracts in the same area.**

Q. **And are you the member of any national committee?**

A. **Yes, I am. Right now I serve as a member of the FDA Advisory, Advisory Committee on Pharmaceutical Sciences and Clinical Pharmacology.**

Q. **Approximately how many years of experience do you have in the study and the design of pharmaceutical formulations?**

A. **I have about 35 years of experience.**

Q. **And that includes experience with, as we discussed, oral pharmaceutical formulations?**

A. **Yes.**

Q. **Have you had experience formulating capsules and tablets and other types of oral pharmaceutical formulations?**

A. **Yes, I have.**

Q. **And are you familiar with formulation design of drugs that have different crystalline forms?**

A. **I am familiar with the need to understand crystalline form of the drug substance and that there are formulation issues involved in formulating drugs that are, that have polymorphic form.**

Q. **And in your experience, do you also have experience with formulating drugs that are considered poorly soluble?**

A. **Yes. I have a propensity to pick poorly soluble compounds when I'm choosing model compounds for my own experimental system, so I've had a lot of experience with poorly soluble materials.**

Q. **And have you consulted with pharmaceutical companies on formulation design or development?**

A. **I have. A number of times I've been invited to meet with the pharmaceutical industry at times where they just want general information about routes of administration and selection of routes. When they have a particular project in mind, we may be discussing formulation aspects or selection. That would be appropriate for a formulation.**

Q. **Thank you.**

MR. ABHYANKAR: At this time, Your Honor, Sandoz would like to tender Dr. Donovan as an expert in the area of pharmaceutical formulation.

MS. ANDERSEN: No objection, Your Honor.

THE COURT: All right.

MR. ABHYANKAR: Let's move to the next slide, 3.

BY MR. ABHYANKAR:

Q. **Dr. Donovan, let's start with an overview of your testimony. Can you briefly walk through what we'll be discussing today?**

A. **Sure. What I'm going to start out with is a bit of a background on pharmaceutical formulations, the preparations described as formulations and their outcome as dosage forms just to give the Court some idea of what it is these terms mean. And then I'm going to talk a little bit about the person of ordinary skill in the art, the typical training**

and background and so forth of somebody who is considered a pharmaceutical formulator. And then I'm going to discuss my opinions about the '231 patent and that my opinion that it's invalid for lack of written description and that it's invalid for lack of enablement.

Q. **So let's start with the background on formulations, and for the benefit of those like me who are not trained as formulators, can you just describe for us what a pharmaceutical formulation is?**

A. **So a pharmaceutical formulation is the drug substance itself, the molecule that is the active drug, and all of the other materials that we combine with that drug substance to give the final, if you call package of drug that we're going to administer to the human. So the final tablet or capsule or cream or patch or gel or any number of various types of ways that we present the drug substance so that it works and gives the effect that is desired.**

Q. **Did you create a demonstrative that walks through the development process that we just discussed?**

A. **Yes, I did.**

Q. **If we can pull up slide 5, please.**

Dr. Donovan, can you walk us through what we're seeing here on this slide?

A. **Sure. So this slide is meant to give an idea, sort of the general category of activities that are used when**

somebody is going to take a drug substance and formulate it into the drug product.

And there are, you know, there are lots of things that go in each of those steps. And at this point, really what I want to make clear is that formulation design is actually -- and formulation itself is actually an iterative process and that's why the arrows go both ways between all of the boxes.

And we could have made this even more complicated by having them move all over the place. But I step forward. I do testing. I get information about what I'm doing and that may cause me to either say that was what I expected and that's the characteristic I'm trying to build into my formulation and drug products, and I'm going to keep moving forward or it may cause me to say, that's not going to work. That's not going to meet my drug product needs, and as a result I am going to have to go back, get different information, test different things to then come up with a next step. So it's a very iterative process is really what the main point of the slide at this time is.

Q. And I notice the title of the slide refers to oral formulations. Is there a reason you have focused on oral formulations for this development process?

A. Yes. I focused on oral formulations because the '231 patent is focused on oral formulations.

Q. **So let's walk through each of these. Let's start with the top.**

Can you explain the design process at the beginning?

A. **Sure. So as a formulator, I get involved in drug product development when there's a drug substance identified that has a particular therapeutic effect that is desired. And we need to be able to present it to humans. And so the formulator again is in charge of taking that drug substance, turning it into a material, a product that somebody can actually administer or take.**

And so we find out about things, well, first, what's the dose of this intended agent? How much of drug substance do we need to deliver? And the disease state might tell us which of the dosage forms are most practical or impractical to select.

And then, finally, what's the patient population that's going to be using this or intended to use it, because that, again, is going to potentially reduce the number of likely dosage forms that we would select.

So as an example, if I -- if my drug substance and my intended disease state is only a disease of small children, I have limited numbers of dosage forms that small children are able to accommodate and so I just, I focus on those.

If I have a broader choice, there's more work that goes into selecting, but at some point in time, I'm going to select the likely dosage form I'm going to work on first or a couple back ups or whatever.

Q. **And let's turn to slide seven. Can you explain what we're seeing here with respect to oral formulations?**

A. **Yes. What I -- I wanted to make the point that a drug product and the dosage form is a distinct composition. So with these three pictures, three forms of Advil. The same drug substance, ibuprofen in all three, but they're presented in different forms.**

So the Advil tablets, the liquid gel system or soft gelatin capsule system and the children's suspension system. And there are different materials that get used to bring about each of those, different production sequences, different quality assurance characteristics for each of them.

And we'll notice that the tablet and the capsule even have the same doseload. Both have 200 milligrams of ibuprofen, but the dose load in the suspension is different. Different patient population, different dose. It actually lends itself to be able to give different doses.

And I apologize that my phone is ringing.

THE COURT: Do you want to go put it on hold?

THE WITNESS: Different doses based on weight

because you can give different volumes.

THE COURT: Do you want to just put it into voicemail or something or you can answer it and have a conversation in front of us.

THE WITNESS: I live in Iowa. I know what that call is about. No.

BY MR. ABHYANKAR:

Q. **Just to confirm, on the slide we're looking at here, these are all considered oral dosage forms or oral pharmaceutical formulations?**

A. **Yes, they are.**

Q. **And are there more than these kinds of oral dosage forms available for a formulator to consider when they're designing drugs?**

A. **There are. There's a tremendous number of potential oral dosage forms. Again, just a selection of what I refer to as immediate release dosage forms, they're intended to be administered and act relatively rapidly.**

There's a whole -- there's a whole bunch of other formulations where we use more of the dosage form itself to control the rate at which the drug gets absorbed and so forth. So there are far beyond tablet, soft gel and suspensions or solutions. There's controlled release tablets. There's a tremendous number of possible oral dosage forms.

Q. **Let's just focus with these three examples for now, but is the approach to designing these different formulations going to change depending on what they are, the tablet versus a liquid versus a gel or capsule?**

A. **Certainly, because we use different material joined with the drug substance to bring about each specific dosage form, so the approaches are different. Sometimes the testing is different, the final manufacturing is different to bring each. To bring each dosage form about requires different activities and different considerations and different materials.**

Q. **So let's go back to slide A, the design pathway. Let's say we go ahead and select our oral dosage form. What do we do next?**

A. **So the design and the choice of dosage can be done initially, and then we have to know something about the chemistry of the drug substance itself, and we're going to rely on that we probably know some things about the chemistry already of the materials we're likely to choose to join with that.**

So we spend time actually understanding the chemistry of the drug substance. So we know which characteristics we might have to build around that not every drug compound, all of the perfect characteristics that we need to have it well absorbed and so forth.

So we try to add material into the dosage form that might help with that or we might add materials into the dosage form that make it even better than it already is. A number of things that we might be able to consider to do. But we still need to know the basics about the drug substance itself. So we conduct what's called pre-formulation testing.

Before we even get to formulation, we're going to understand the chemical properties and the physical properties of our drug substance as best we can so that we know how to design the best acting formulation for the desired use.

Q. **So let's talk about some of these pre-formulation studies. Turn to slide 9, please. What type of testing do you consider as a formulator?**

A. **Okay. So what I've put on the slide is a variety of what people would consider pre-formulation tests commonly get done to evaluate the chemical or physical properties of the drug substance.**

There are others, but these are certainly the most -- many of the most common activities and I'm just going to highlight a couple of them starting with the aqueous solubility of the material itself. And that's a really, really important thing for a formulator to know because one of the cardinal rules of drug absorption is that

the drug molecule itself has to be in solution in order for it to get absorbed.

So for gastrointestinal absorption or for nasal absorption for that matter. My drug molecule has to be in solution in the liquids that are present at that absorbed surface, the mucosal surface, my nose or gastrointestinal tract, wherever. It has got to be in solution.

And so the contents of the gastrointestinal tract are primarily water, some other substances, but we're going to worry about aqueous water solubility. And because the gastrointestinal tract has different pH's, stomach, very acidic in most individuals, and as we move through the rest of the intestinal tract, more neutral, light in character. The solubility of drug substances changes as a function of pH, so I'm going to want to know what the solubility is in those major characteristic regions of the gastrointestinal tract also.

So solubility is very important. Dissolution rate is how fast does that material actually dissolve, because, again, if I want a rapidly acting drug, I like my dissolution rate to be fast so I can accomplish that. I want it to go in solution quickly in the environment where it's going to be absorbed.

The partition coefficient tells us the relative solubility between a liquid-like substance and an

aqueous-like substance. So it tells us something about how well the drug might be absorbed once we present it to the absorptive membrane.

Polymorphism. We've been hearing a lot about polymorphism. It's certainly important to know about the drug substance, whether there are polymorphs, which polymorph is being used. Crystallinity, also an important characteristic.

I'm going to move through the rest of those details and studies. They're important, but I really want to focus on chemical stability as a formulator. That's one of my cardinal goals, is I like my drug product to be stable and give a product lifetime shelf life of several years, again, for convenience of our users, that they don't have to go and get their prescription filled every day because we didn't make it chemically stable.

So chemical stability of the drug itself is something that that I interrogate during pre-formulation testing because there may be material that I can include in my dosage form, inactive ingredients or excipients that we call them that I can include in the dosage forms itself that slow down those degradation pathways. It would be nice if we believe they would eliminate them, but at least slow them down enough, limit their current that I can actually have that long shelf life that I desire from my pharmaceutical

product.

Q. **Thanks.**

And we talked, you talked about polymorphism and crystallization and aqueous solubility. Is it your understanding based on your experience that the aqueous solubility of one crystal form of a drug product, or drug substance can be different than another?

A. **Absolutely, certainly. That's a characteristic of different polymorphic forms, is they have different solubility characteristics.**

Q. **And based on those differences, does that impact the design of the formulation that you are looking at?**

A. **Certainly, certainly, because, you know, we need adequate solubility in the time frame that the drug product and drug itself are present at the absorptive site so they can get absorbed. So they can go into solution and get absorbed. Yes, it's an important part of formulation.**

Q. **Right. So let's go back to the pathway slide, slide 10. You selected the dose form, we've conducted the pre-formulation tests and now we move to the next step.**

Can you explain for us what we're doing here?

A. **Sure. So in the next step, I start to combine my drug substance with some of the inactive ingredients or the excipients again that I think might be useful in my formulation. And the reason I do that, I do that -- I may**

start to build up multiple components and so forth. Each of my inactive ingredient or excipients is also accountable. It has properties, too. It has chemical reactivities, too, and I want to make sure both that my excipients are compatible with my drug substance, they don't cause things to happen with my drug substance that I don't want to have happen and that they're actually adding in the characteristics that I want them to add into my formulation and to get me to the desired characteristics of my final dosage form.

So I do some work where I'm identifying excipients, I'm looking at the combination and what their behavior is and I'm still thinking about stability and so forth, but in the combined stage, I'm essentially interrogating the excipients and the ability to make the dosage form that I want to be able to make.

Q. And can these inactive ingredients or excipients, can they serve different purposes in a formulation?

A. Oh, absolutely. You know, even each material itself might be able to serve multiple purposes. We have a variety of excipients that we have choices of and they each have particular characteristics.

Unfortunately, some of them even have limitations that we then also have to formulate with or around, that they act so well in one aspect, we continue to

include them in the formulation, but we know they have some negative aspect and so we actually have to add some others potentially or do something with our formulation to try to counteract that as best as possible.

Q. So claim 27 identifies some excipients; right?

A. Yes, it does.

Q. And so why don't we just pull up JTX-11 and turn to claim 1.

Can you walk us through the types of excipients that are claimed here?

A. Yes. So in claim 1, we'll look at B, C, D and E. Those are the excipient classifications that are being described by the claims.

So there's a diluent classification and a range of amounts of materials that we would add a diluent and then disintegrating agents is another category. Surfactants is a third category and lubricant as a fourth category. Each of those categories has multiple agents that are reported to act in those ways, but in claim 1, it's just describing the categories of excipients that should be included.

Q. So let's talk about those categories. So we can move to slide 11.

Let's start from the top, the diluents. Can you explain for us what a diluent is and what its function is in a pharmaceutical formulation?

A. **Sure. So the diluent itself, and they have it described on the slide as a filler. It's essentially meant to bulk up my drug substance into my dosage form. The drug substance is oftentimes high potency. A few milligrams worth of drug substance is what I want to administer to my user, and a few milligrams is way less than a quarter of a teaspoonful.**

So those very small amounts of material are very hard for individuals to manage and dose accurately. We add some bulk so that they're physically easy to handle and manipulate and manufacture. The diluent serves that purpose, to dilute up the active drug substance to give us enough mass or volume in the dosage form so that it's handleable and manufacturable and that we can assure that we have equal doses of drug, too, for each unit that we desire.

Q. **How about the next one, disintegrants. What are they used for in a pharmaceutical formulation?**

A. **So disintegrants are used to help with drug dissolution, and so in the case of an orally administered drug for the gastrointestinal tract delivery system or dosage form, we'll take a tablet as an example.**

You know, I've taken a solid, I've taken powders, I've compressed them and somebody has swallowed them. Once it's in the GI tract again, do I want that to be

rapidly acting? I'd like all of the drug to dissolve a lot of that as quickly as possible, but in my compact and solid tablet, that doesn't necessarily happen very quickly off of the surface of the tablet.

So what I do, I include material that causes the tablet once ingested to break apart into much smaller pieces. Lots of smaller pieces give me lots of more surface area and interaction and my drug can dissolve out of those smaller pieces. Total amount of drug can dissolve. You get more and faster dissolution from the smaller pieces than from a single tablet.

So we disintegrate the tablet or whatever dosage form that we put that in to again accomplish that making smaller pieces so that the drug is more available to be put into solution.

Q. **All right. What about surfactants? I see a Dawn bottle there. Can you explain what surfactant is?**

A. **The Dawn bottle is to show we're all very familiar with surfactants and we're more and more familiar with surfactants. They are the materials that are in soaps and they are included in soaps because in my dish washing example, they take the grease off my dishes and allow the grease to be dispersed in water and go away in the case of Dawn.**

In the case of a drug substance, a

low-solubility, hydrophobic water-hating drug substance, my surfactant is able to interact with that hydrophobic drug substance and it's able to disperse it into the water content that in my gastrointestinal tract, for example, and thus it allows me to get the drug to the -- the absorptive surface as a molecule that can be absorbed instead of as an insoluble solid that will just pass through the gastrointestinal tract.

Q. **Finally, I see lubricant at the bottom. Can you talk about what the purpose of a lubricant in a pharmaceutical formulation is?**

A. **The lubricant is primarily a manufacturing aid. We make our pharmaceutical dosage forms on sophisticated piece of equipment. We oftentimes like to make lots of them rapidly so we can provide the world supply of our drug product.**

And the lubricant is added to allow the colors to flow through those processing pieces of equipment and not jam them, not get stuck on edges, not jam up the production equipment and so forth, to leave from being compressed potentially as a, as a full beautiful tablet compared to a chipped mess.

A number of reasons why we want to keep material that would have the ability to seize up or gather together because of frictional forces, we'll add the lubricant in

there just to keep the process moving.
Q. How many different types of lubricants are there?
A. Oh, there's quite a few. At least a couple of dozen types of lubricants that commonly get used and there's surprising material that we use as pharmaceutical lubricants. They're not -- they're not -- they're typically not similar to the kind of lubricants we think of for automobiles or anything else like that. They're other substances that give lubricating processes characteristics in most of our pharmaceutical processing equipment.
Q. And if we could pull up slide 12.
Are these examples here of lubricants that are described in the '231 patent?
A. Yes. This is a section in the specification that identifies some suitable lubricants or glidants. You can see there's a set of long list of materials that have been identified as having lubricant properties.
Q. Do all of these lubricants behave the same way when included in the same amount in a pharmaceutical formulation?
A. No, they don't, because, again, each one of these is a different chemical substance. They may, in a general mechanistic standpoint, some of them may act similarly to others, but, again, each individual material has its own characteristics and needs to be evaluated based on its own

characteristics, both its lubricant characteristics and whether they are sufficient enough at what concentration we need and potentially on whether that build in any other characteristics to our dosage form.

Q. **And if we can go back to slide 11. Can the choice or even the combination of these excipients here have an impact on how the drug ultimately will behave in the body?**

A. **Absolutely. I mean, that is formulation design and drug dosage form development. It's determining what the combinations of materials are and the quantities of each of those materials and maybe even the manufacturing steps, the order of addition of those to allow us to make the final product that we desire, that gives the characteristics that we identify on our drug product to have.**

Q. **And can using different levels or amounts of these various excipients have an effect on the drug product as well?**

A. **Sure, absolutely. It's the relative amount of materials relative to the other material potentially, or the absolute amount of a specific material also. They all again lend to the overall characteristics of the now mixture, but each one of them contributes characteristics and those characteristics certainly are influenced by the amount that we include.**

Q. **And focusing on the lubricant at the bottom, can**

varying the amount of the lubricant, can that have an impact on the properties of a formulation?

A. **Certainly. The amount of lubricant is potentially one of the challenges that pharmaceutical formulators face. Again, we need the lubricant. They're a manufacturing aid. They allow us to actually produce the dosage form that's designed, but a number of the lubricants are hydrophobic in nature, so, again, water-hating in nature. It helps them maybe act well as a lubricant, but they also can give a hydrophobic nature to our dosage form, and as a result we start building in a water-hating into the dosage from, which in most cases is a negative, because, again, we want it to interact with water so the drug can go in solution so the drug can get absorbed.**

Q. **Let's go back to the pathway slide again. Now that we've identified our excipients in the dosage form, what do we do next?**

A. **So we've identified the excipient and we actually develop and design and test the prototype formulation combinations that we identify. We make them and we make them because they're multicomponent mixtures. They often contain materials that have multi-functions to them and we actually need to test them to make sure we built in the performance characteristics that we had intended, and so we make our formulations, the ones that we think are going to**

be the best.

We learn from the results and we may need to go back to our combination state and re-evaluate, select different excipients potentially, or we may be able to move forward. It's very much a process of testing and evaluating the results based on what the performance characteristics of the dosage forms desired had been identified to be.

Q. **If we can move over to slide 14. Are these some of the testing criteria that you look at this stage?**

A. **Yes. There's only a few identified. There's more. Some of them are testing criteria. But these are some of the key aspects that we almost always look at in a prototype formulation as we're determining whether we can move forward.**

The first one, if it's a dosage form that we want to disintegrate to enhance the ability of the drug to dissolve, we're going to look at the disintegration rate. We do that in the lab. We have systems that have been developed and accepted that we think have some meaning regarding how the drug product itself is actually going to perform and disintegrate in the body. So we need laboratory testing equipment for the disintegration.

The dissolution profile is the rate at which the drug substance dissolves out of those particles. We have disintegrants, if we don't include a disintegrant for doing

a controlled release.

Oral dosage form, we have different criteria for the rate of drug dissolving that one would look at. But common testing to evaluate, to make sure that our formulation is going to give us the solution of drug at the absorption site that we desire and we also are looking at evaluating the chemical stability of the drug substance and of the components we've now added to that to make the dosage form.

And we're also making sure that the whole composite in the material are physically stable. We don't want the -- want form changes of our material during the shelf life. That has been a problem for a number of drug products, and so we continue to monitor and test the physical stability of the components in addition to their actual chemical stability.

Q. **And, finally, if we can go back to the pathway slide. Can you briefly describe what the last step is and what we look to there as formulators?**

A. **Sure. So I've developed a formulation and now I've developed a formulation that is meeting my test criteria dissolution rate, disintegration rate, so forth, and chemical stability for the period of time that I need. Well, I need to actually test that in my, hopefully, my human subjects because my laboratory test systems, again,**

are somewhat reflective of what we think might happen, but we actually need to test that the formulation as made actually gives the desired performance, that it meets the blood concentrations that I need at the time I need them to treat the disease that this whole dosage form and drug substance are intended for.

So we oftentimes end up having to reformulate based on what we've learned once we've administered the drug product, that we need to change the formulation, to change some of the behaviors to actually give the therapeutic desired performance.

Q. **Right.**

MR. ABHYANKAR: Your Honor, we're concluding the background section. It looks like lunch might be a good place for a break.

THE COURT: Here's what I'm thinking, looking at your PowerPoint. Do you want to briefly hit definition of POSA, because I guess you're going to tell me at the end of the day, it doesn't matter.

MR. ABHYANKAR: That's exactly right.

THE COURT: Why don't you do that. If you could do that in less than five minutes?

MR. ABHYANKAR: We think we should be able to do that. Can we move onto the next slide.

BY MR. ABHYANKAR:

Q. **And, Dr. Donovan -- actually, let's us pull up slide 17.**

Do you offer a definition for a person of skill in the art in this case?

A. **Yes, I did.**

Q. **Is this a summary?**

A. **Yes. The background of the POSA that I designed and the POSA has a significant amount of technical and scientific education, so education in chemistry or engineering or pharmaceutical sciences primarily, experience in formulating pharmaceutical products, and then a familiarity with the excipients or inactive ingredients, so that they can act as an independent formulator and we can go back and forth about level of education versus experience and so forth, but it's that combination of basic education, experience, understanding of the materials that could be selected that makes a formulator.**

Q. **And are you aware of plaintiffs' expert, Dr. Williams' definition of a POSA?**

A. **Yes, I am.**

Q. **And let's pull up the next slide, please. And does this reflect a summary of his definition in the case?**

A. **It does. It's my summary of his definition, slightly different than mine.**

Q. **Although different, do your opinions turn on which**

definition of a POSA the Court adopts?

A. **No, my opinions do not depend on the other definition.**

Q. **And would you qualify as a POSA? Would you qualify as a POSA under either definition?**

A. **Yes, I would.**

Q. **Great.**

THE COURT: Okay. That's a great place to stop. Good timing. And I will see you all at 1:00 o'clock.

MR. ABHYANKAR: Thank you.

(Luncheon recess taken.)

- - -

Afternoon Session, 1:00 p.m.

THE COURT: Okay, everyone. Are you all there?

MR. ABHYANKAR: Yes, Your Honor.

THE COURT: Great. All right. Mr. Abhyankar?

MR. ABHYANKAR: Thank you.

BY MR. ABHYANKAR:

Q. **Dr. Donovan, in we could pull up slide 19. I would like to turn to your opinions regarding written description, and first I would like to briefly discuss the standards you applied in this case with respect to written description.**

So if we could pull up slide 20, please.

I understand you are not a lawyer, Dr. Donovan, so in your own words, can you explain for us what you understand the standard to be and how you applied it in your

analysis in this case?

A. **Sure. So my understanding of the standard for written description is that the patent specification has to tell a POSA that the inventors had invented or possessed the full scope of the invention or the claim.**

Q. **Right. So let's talk about that invention. If we could pull up JTX-11, please, of the '231 patent.**

And I'd like to pull up -- actually, let's just go to slide 21. Let's pull up claim 27. Thank you.

And, Dr. Donovan, just to confirm, is it your understanding that this claim, claim 27, is the sole claim of the '231 asserted against Sandoz in this case?

A. **Yes, that's my understanding. It's a dependent claim on claim 1.**

Q. **And is claim 27 a dependent or independent claim?**

A. **Yes, it's a dependent claim.**

Q. **What claim does it depend from?**

A. **Claim 1.**

Q. **Looking at this claim here, how would you describe the scope of this claim?**

A. **Extremely broad. Just reading the first line tells me that it's very broad, pharmaceutical formulation for oral administration.**

Q. **So let's start there. If we can move to the next slide.**

Can you explain why a pharmaceutical formulation for oral administration makes this claim broad?

A. **Well, it allows for any possible dosage form or delivery form administered via the mouth orally. So all forms of tablets and capsules and gels potentially and, you know, controlled release, immediate release, any possible dosage form that I would put into the mouth could be or is part of the invention.**

Q. **And does the '231 patent list a number of examples of oral dosage forms that would fall within the scope of claim 27?**

A. **Sure. They give, you know, twentyish or so examples and some of their examples are broad categories, that there would be far more subsets of those from a formulator's definition of the dosage form.**

Q. **So if we could pull up JTX-11, the '231 patent, column 43. JTX-11, please, column 43.**

Is this the description you were referring to, Dr. Donovan, about the dosages of oral dosage forms that would fall within the scope of 27, claim 27?

A. **Yes, it is.**

Q. **Are these all of the oral dosage forms that would have been available to a POSA as of June 4th, 2012?**

A. **No. There are plenty of additional possible oral dosage forms beyond what's listed in this column.**

Q. **All right. And if we could turn back to slide 22, please. Is there anything else about this claim apart from the fact that it covers any oral dosage form that makes it broad in your opinion?**

A. **Yes. Even the following points A through E also add to the breadth of the claim. So the description of component A ibrutinib also broadens the claim because it allows for any form of ibrutinib. So any crystalline form, amorphous form, any other form that ibrutinib is available as or could be available as is covered or included in the claim.**

Q. **So without limiting it to any particular form of ibrutinib, and I believe you testified about this earlier, but does the form of ibrutinib, will that impact how a formulation will act or how you would design a formulation for a particular drug?**

A. **Certainly, especially ibrutinib with polymorphic forms. Each of those polymorphic forms has its own chemical property. Solubility is one of the most important ones and solubility differs among the polymorphic forms as could stability, as could a number of other characteristics that we need to manage or manage around in drug, in drug formulation.**

Q. **Great. Apart from the fact that this claim covers any oral dosage form and any form of ibrutinib, is there**

anything else about this claim that indicates that it is broad to you?

A. **Sure. Even, even in claim 27, where the diluent has been identified as microcrystalline cellulose, where the disintegrating agent has been identified as croscarmellose sodium and the surfactant has been identified as sodium lauryl sulfate. Even with the identification of those three compounds, each of them is able to be used in a broad range of composition in the dosage form, and so, again, it lends to being able to do multiple different combinations, other combinations and so forth along with all of the other forms of ibrutinib and we're just continuing to span the breadth and the number of potential formulations that claim 27 describes.**

Q. **So is your understanding that Dr. Williams has opined that because claim 27 identifies specific excipients for the diluent, disintegrating agent and surfactant, that this claim is actually narrow?**

A. **I'm aware Dr. Williams has stated that. I don't agree with that just because we've identified three of the materials to be included in the formulation, there are still a vast variety of possible formulations, all of the oral administration formulations, for example, that it doesn't -- it is still extremely broad.**

Q. **Is there anything else about this claim that makes it**

broad to you?

A. **If you go back to claim 1, claim 1 requires one or more lubricant, and so I both have the opportunity to bring together a combination of lubricants, which, again, expands the potential number of formulations that are covered by the claim and it doesn't claim a range for lubricants.**

So I could utilize any amount of lubricant within the context of the rest of the claim. And you can calculate that there would be a maximum range based on the definitions of the amounts of the other compounds, but one or more lubricant at a range of levels, broad possibilities for formulations that would -- that are defined by this claim.

Q. **And as of June 4, 2012, would a POSA have had, I believe you said dozens of lubricants available to them for use in a formulation as described in claim 27?**

A. **Yes, they would have. There are dozens of materials that could be used as lubricant.**

Q. **Now, you said there is no calculation range specified. You've been able to calculate one, the maximum range. I would like to turn to the next slide, slide 27. And can you walk us through how you came up with this number?**

A. **Sure. So claim 1 and claim 27 give ranges for the materials that are to be contained in formulation, meaning the components of claim 27, and what I did was take the**

lowest amount of each one of those ingredients, so the lowest amount of ibrutinib, the lowest amount of microcrystalline cellulose, croscarmellose, sodium lauryl sulfate, and I can account for 85 percent of my formulation.

So at least amount of formulation, the diluent is forty percent. The least amount of ibrutinib that can be contained in the formulation is 40 percent -- two percent for the surfactant, three percent for the disintegrating agent.

So 85 percent of the formulation has been accounted for by those, those materials, which leaves up to 15 percent that a formulator can add one or more lubricant to the formulation up to that amount and be within the claim.

Q. **So you've established that claim 27 allows for 15 percent. Does the specification of the '231 patent disclose anywhere a formulation that could have 15 percent lubricant in it?**

A. **No, the specification doesn't, doesn't describe anything close to 15 percent lubricant in a formulation.**

Q. **And for purposes of formulations that match the elements of claim 27, what is the maximum amount of lubricant that's used in those example formulations?**

A. **One percent.**

Q. **One percent. Well, let's take a look at that and the**

examples described in the patent. Let's pull up slide 28, please.

Dr. Donovan, can you explain for us what we're looking at here?

A. **Sure. And this is a rather complicated slide and the slide that follows is in the same format, so I will take a few moments to describe in general what's being shown here.**

So we'll look at the columns first, the column labeled ibrutinib formulation, column labeled crystalline ibrutinib, crystalline form A of ibrutinib. Underneath those in the column are general formulation example descriptions that are in the specification.

So there's one set of example descriptions that utilize ibrutinib as the drug substance. There's another set that are formatted and almost exactly the same except require crystalline ibrutinib and then there's finally another step that, again, formatted almost entirely the same that requires the use of crystalline A as the ibrutinib component.

So that's what I have in the rows. So if we look at the lightly shaded background row, you'll see that the description of the pharmaceutical formulation is the same in each column within that row except for the ibrutinib or crystalline ibrutinib or crystalline form A, and all the

rest of the examples are set up the same way, that all of the rows, the descriptors of the general formulation are the same across the types of ibrutinib, just differ by types of ibrutinib.

Then what I also added was a highlight for the amount of lubricant that was described in each of the examples, so in the case of the first row, one percent of a lubricant. In the second set of examples, one percent of magnesium stearate, which is a well-known lubricant material.

Q. **And to confirm, do any of these examples limit the type of oral dosage form that is being described?**

A. **No. They all describe a pharmaceutical formulation for oral administration. So all possible oral formulations or oral delivery systems.**

Q. **All right. And then if we could turn to slide 29, please.**

And similarly, what are we looking at here?

A. **So the table is set up the exact same way. The column about crystalline is the drug substance. Crystalline form A is the drug substance. And then across the row, the same generalized formulation example. And it has highlighted the amount of lubricant that is included in that particular example.**

So the first example, one percent of magnesium

stearate. The second example, .5 percent magnesium stearate. And in the third example instead of percent, the actual math values of the particular component is described in that example, but it describes a formulation for oral administration and its component.

Q. **And to confirm, for this slide, for these examples, again, is there any specific oral dosage form that's recited in any of the examples?**

A. **No. In all of the examples that are described in this table, they are all described as a pharmaceutical formulations for oral administration comprising these components, all possible dosage forms.**

Q. **And as a reminder, you know, you've talked about how some of these examples pertain to crystalline ibrutinib or crystalline form A. Claim 27 is not limited to any particular form, whether crystalline, amorphous or anything else; right?**

A. **That's correct, ibrutinib in any form.**

Q. **Right. I'd like to turn to Table 5 in the patent. Dr. Donovan, what are we looking at here with respect to Table 5 and what it's telling us about the formulation?**

A. **Okay. So Table 5 is describing capsule formulation and the way Table 5 is set up, it gives the materials that are included in the formulation in that left column, so crystalline compound 1, crystalline ibrutinib,**

microcrystalline cellulose, croscarmellose, sodium, sodium lauryl sulfate, magnesium stearate. The exact same materials that were in that when the materials were specified, the same material identical to the previous set of examples. And in this case, what is being described is specific capsule formulation containing different amounts of ibrutinib. And so 40 milligrams ibrutinib, 140, 140, 200, and then the component of component of the formulation both described in weight percent and also described in absolute math of that specific material included in that capsule.

Q. **Right. So let's turn to slide 30.**

How many of these formulations actually match up with claim 27?

A. **Okay. And there's actually only one of these formulations from Table 5 that matches the specification in claim 27 or the sub-claim in claim 27. And I highlighted a bit on Table 5 to make it a little bit easier to follow what I'm talking about.**

And so the light blue background column, that's the formulation that met the requirements of claim 27 and the boxes that I've placed over the table are a reminder of what the, what the claim tells us we can include.

So the claim specified between 40 and 50 percent diluent is possible in the formulation. The shaded 140 capsule meets that. The other examples do not. And then

the -- claim 27 and claim 1 allow for any amount and if you do the calculation, up to 15 percent of the lubricant, in this case, magnesium stearate, and the blue shaded example is the only example that contains a lubricant and it contains it at a level of 0.5 percent.

Q. **And if we could turn to Table 6, please, in the '231 patent.**

THE COURT: Can you do me a favor? Can you hold for one second?

MR. ABHYANKAR: Yes. Yes, Your Honor.

THE COURT: Okay. Thank you. Sorry about that.

MR. ABHYANKAR: No problem.

BY MR. ABHYANKAR:

Q. **Dr. Donovan, let's turn to Table 6 in the '231. We'll blow that up for her.**

What are we looking at here?

A. **So this is an example provided in the specification that describes a general formulation, describes a general formulation, components for a tablet.**

Q. **Okay. And so Table 5 was about capsules and Table 6 is about tablets.**

Table 6, the formulation described here, does it match up with claim 27?

A. **No, it doesn't.**

Q. **And --**

A. **It --**

Q. **Sorry. Why not?**

A. **Claim 27 requires the inclusion of sodium lauryl sulfate. There is no sodium lauryl sulfate contained in this example formulation.**

Q. **And, in fact, there's no surfactant listed at all. Correct?**

A. **Right.**

Q. **And although this particular formulation doesn't match up, what is the high end range of a lubricant that's included in the formulation?**

A. **So they specified up to 2.5 percent magnesium stearate, which is again lubricant material.**

Q. **All right. Now, other than the examples that we've just talked about, are there any other formulation recipes that are identified in the specification? So other than Table 5 and Table 6, any specific formulation recipes identified in the specification of the '231?**

A. **No, there aren't.**

Q. **The description in the example that we have looked at, are they broader or narrower than claim 27?**

A. **They're all narrower than claim 27.**

Q. **And why is that?**

A. **Well, they're either specifying that it's a capsule or a tablet or they limit or don't even include a lubricant.**

Much lower components of the lubricant compared to the 15 percent. That's what the claim specified.

Q. **And does claim 27 permit up to 15 times the amount of lubricant than the highest amount that's described for the formulations that match claim 27 in the '231?**

A. **Essentially. So the one formulation, the specific formulation declaring the components and their amounts describes one percent magnesium stearate lubricant. So you can have up to 15 percent, essentially 15 times.**

Q. **So based on this -- well, let me ask you this question: Does the specification of the '231 patent describe any oral pharmaceutical formulation of ibrutinib that includes a lubricant that is up to 15 percent --**

THE COURT: Actually, can I stop you for a second? Hold on. I'm confused.

MR. ABHYANKAR: Sure.

THE COURT: I thought that the amount that you identified on slide 30 had .5 percent lubricant. How do you get one percent?

MR. ABHYANKAR: Oh, sorry. Your Honor, as we established earlier, if you can go back one more slide.

THE COURT: Those are one percent. Right? I get that.

MR. ABHYANKAR: Yes. So --

THE COURT: But it's as low as .5 percent in

Table 5. Right?

THE WITNESS: Can I -- would you like -- can I explain, Judge?

THE COURT: Yes. Could you, please?

THE WITNESS: Sure. If you at the slide deck as it appears right now, the top row also discloses components that would -- it also discloses components, but what it's disclosing is one percent magnesium stearate.

THE COURT: And I get that, but I thought he asked you the most that's disclosed in the patent and I thought you said one percent. Am I missing something? I probably am. I'm probably missing something, so what am I missing?

THE WITNESS: The specific table in Table 5 is really a specific example, a dosage form plus the component, and they meet the requirements of claim 27, and you are correct, it's at .5 percent.

More general, yet still could meet the requirements of claim 27, up to one percent is described in the specification in the example.

THE COURT: Okay. All right.

THE WITNESS: You are correct, the exact specific example that's provided is .5 percent.

THE COURT: Okay. Sorry. Go ahead.

MR. ABHYANKAR: Sorry, Judge Connolly.

THE COURT: No. Go ahead.

BY MR. ABHYANKAR:

Q. **To follow up and to make the record clear, what is the difference between this formulation that we're seeing here at the top and the formulation, the specific example that's in Table 5?**

A. **So in the, the -- the example that has been pulled out on the opposite slide, it allows for any oral formulation or any pharmaceutical formulation for oral administration. Table 5 is limited to capsules only.**

THE COURT: All right.

BY MR. ABHYANKAR:

Q. **All right. And just to confirm, the specification does not describe any oral pharmaceutical formulation with a lubricant content up to 15 percent; right?**

A. **Correct. There's no description of a formulation with a lubricant up to 15, at the level of 15 percent.**

Q. **And is there any evidence in the specification in your opinion that shows that the inventors actually invented a formulation of ibrutinib that had lubricant up to 15 percent?**

A. **No, there's no description in the specification that would lead a POSA to understand that they had invented a formulation with that high a level of lubricant, the 15 percent.**

Q. **All right. I'd like to -- and so what is your conclusion, what is your ultimate opinion regarding lack of written description with respect to claim 27 of the '231 patent in view of all of this?**

A. **Well, I view that claim 27 is invalid based on the lack of written description provided in the specification.**

Q. **So let's turn to slide 34 and your enablement opinion.**

So let's start again and I will reiterate, I know you're not a lawyer, but just in your own words, can you explain, we'll turn to slide 35, can you explain what you understand the enablement standard to look at or analyze?

A. **Sure. So the enablement standard requires that the specification has to communicate to a POSA how to make and use the full scope of the claim, and then without undue experimentation, that there has to be information provided that assists the POSA to, with their knowledge, make the invention.**

Q. **And did you analyze the number of factors called the Wands factors to determine whether undue experimentation would be required to practice the full scope of claim 27?**

A. **I did, yes.**

Q. **All right. Let's look at these factors. Go to the next slide, please.**

So let's -- are these the factors that you

analyzed, Dr. Donovan?

A. **They are the factors I've come to know as the Wands factors.**

Q. **All right. And we've spent a fair amount of time on the breadth of the claims, so maybe let's start there.**

We'll highlight that. And just a reminder, how does the breadth of this claim suggest to a POSA whether undue experimentation is required to practice the scope?

A. **As I discussed, claim 27 is extremely broad, contains a world of possible oral formulations, and as a result to actually bring about all of those oral formulations under all the variables that they could address.**

You know, any oral dosage form, any form of the ibrutinib, the ranges of multiple of the components, it would just take a huge amount of experimentation to address the breadth of the claim.

Q. **And let's turn now to the nature of the invention. Go back to slide 38 -- sorry. 36, 36.**

So could we highlight number four, please? Let's talk about the nature of the invention.

How would you characterize the nature of the invention that's recited in claim 27?

A. **Well, it's pharmaceutical formulations for oral administration, extremely broad to begin with. Lots of possibilities, containing ibrutinib material that contains**

or is known to be in multiple polymorphic forms. So it's a complex invention, broad and multifaceted.

Q. **If we could turn to slide 40. We've already discussed this at length. Are these two of the reasons why you believe the nature of the invention is complex?**

A. **Right. It covers, again, all of the dosage, all of the possible oral dosage forms, any form containing ibrutinib, and specifically leading to or could contain up to 15 percent of a lubricant. It adds to the complexity of the formulation.**

Q. **And why does adding up to 15 percent of the lubricant add to the complexity?**

A. **Because, again, many of the lubricants that are used in pharmaceutical composition have some negative aspects to them also, limit some of the performance characteristic of the final dosage form, so magnesium stearate in specific has some limitations that would make including 15 percent of that difficult and still have the dosage form to be able to be utilized and deliver the drug that is contained within it.**

Q. **These issues that you are talking about with respect to the lubricant, are they reported in the scientific literature?**

A. **Yes, they are.**

Q. **If we could turn to DTX-2261, please. What are we**

looking at here, Dr. Donovan?

A. So we are looking at the cover of a reference text called the Handbook of Pharmaceutical Excipients, and this is a commonly used reference text used by formulators, used by educators. I use this with my students. It contains monographs, short descriptions, several pages of description about commonly used excipients and gives us the highlights of their physical properties, how they get used, things that are -- information that will be useful to the formulator when selecting an excipient to use.

Q. If we could turn to page 404 of this text. Can you describe what we're seeing here?

A. Sure. We're seeing the first page of about a four page monograph describing magnesium stearate, the lubricant that has been used in the example in the patent.

Q. And if we could turn to page 405, I would like to call out the comments on the bottom right.

Can you -- what does it say about magnesium stearate as used as a lubricant in a formulation?

A. So this is communicating what POSAs are familiar with about magnesium stearate. It's a hydrophobic material. It has some water-disliking characteristics. As a result, you put it in a dosage form, solid dosage a form in the description here, that you should use the lowest possible concentration to do that because it will give what people

tend to often refer to as a waterproofing characteristic to the dosage form. It makes the dosage form hydrophobic. It doesn't interact with water as well. The drug doesn't dissolve as well, and it goes on to describe capsule dissolution in particular being sensitive to the amount of magnesium stearate. Again, use the lowest amount possible.

And then the mixing time. Mixing the powders to make sure they're all evenly mixed and everything is evenly distributed before we actually make the capsule requires some time. The longer we do that, the more the magnesium stearate is able or presents itself in that hydrophobic manner and then decreases the dissolution of the drug substance in the final capsule.

Q. So based on all of this, the fact that the claim covers any oral dosage form and covers up to 15 percent lubricant, once again, how would you describe the nature of the invention here?

A. Complex. To be able to manage to meet the, the claim requirement and be able to formulate a 15 percent lubricant, for example, and all of the possible ibrutinib forms, the polymorphic forms described in the patent, it's just -- it's difficult and complex.

Q. What is the practical effect of a lubricant being in such a high amount in a formulation?

A. Well, it usually causes the formulation to fail. And

those are, you know, formulator criteria that if it won't allow my drug to release or be dissolved at a rate that will give me the blood concentrations needed, my dosage form has failed. In many cases, that high a level of lubricant, depending on with an oral dosage form I would be making, I might not even be able to make it correctly. It might -- it might segregate. It might not compact well. It might cause coating material to not adhere.

There are a variety of problems that could be encountered with that high a level of lubricant in the, in the formulation.

Q. Okay. Thank you.

Let's turn to slide 36 again, and we'll move to the next, and I'm going to group these together because they are pretty related. Numbers 2 and 3, the amount of direction or guidance presented and the presence or absence of working examples. We talked a little bit about this earlier.

But can you identify for us, what guidance in the specification is there to a POSA to practice the full scope of claim 27 without undue experimentation?

A. Well, again, extremely limited guidance provided by the specification. The claim allows for, again, any possible oral formulation and there isn't any direction provided about almost all of the possible oral formulations

or oral -- formulations for oral administration.

And as we just discussed, there's one working example provided, the capsule with the exact content. One single working example provided. It provides an example that doesn't come anywhere close in lubricant level to the lubricant level described by the claim.

Q. **And that working example is only one of the many oral dosage forms that are otherwise covered by claim 27?**

A. **Right. It describes capsules, but, again, there's at least 20 identified by the, in the specification and there's more, quite a few more if you really would have a formulator to find all of the possible oral formulations.**

Q. **And if we could pull up slide 43 and 44, Mr. Ferrare.**

Just to confirm, these other disclosures that we looked at, did they help provide guidance to a POSA as to how to make and use the full scope of the formulations that fall within claim 27? Please start with 43. Sorry.

A. **No. Again, they allow for a pharmaceutical formulation for oral administration and they, again, repeat the components, the ranges of the claim, and when they do get specific about the material and the amount, they end up being the exact same material as given in the capsule example in Table 5. And so they don't do anything more besides open up the possibility of every pharmaceutical formulation for oral administration as compared to Table 5,**

which are capsules.

Q. **And given what we've learned about the properties of lubricants and formulations and their use, what kind of guidance would you need as a POSA to develop a formulation that has 15 percent lubricant?**

A. **I would need a lot of guidance actually. Fifteen percent of a lubricant, 15 percent of any lubricant, 15 percent of any combination of lubricant, that information is not available in the art of how to formulate and develop a dosage form with lubricants at that level.**

And so that's the information I would need in the specification, how would I make a compact product that would stick together or would dissolve correctly or how can I make sure that all of my coating material will stick to the surface or, you know, again, a whole variety of other problems that we know can be associated with lubricant inclusion in a formulation, I need to know as a POSA at 15 percent how do make that, how to -- yes, how to make that.

Q. **Are you aware that plaintiffs' expert, Dr. Williams, suggests that there are physicochemical properties disclosed in the '231 that would help to fill in the gap for the lack of guidance in the specification?**

A. **I'm aware that he is -- has --**

MS. ANDERSEN: Your Honor.

THE COURT: Hold up. Okay. Hold on. Hold on.

THE WITNESS: Judge, are you waiting for me to answer?

THE COURT: No, I'm not. I'm trying to do something myself.

Okay. Go ahead, Ms. Andersen.

MS. ANDERSEN: Dr. Williams will be testifying later in this trial. Mr. Abhyankar, I believe this is the second time is characterizing his testimony in a certain way. I don't think it's appropriate to do that before the testimony comes in.

THE COURT: So this has been actually the practice to date for the first two days of trial. Everybody was doing that without objection.

Are we planning on having rebuttal in this trial?

MS. ANDERSEN: Well, Your Honor, you had offered defendants a fourth round and you had mentioned true rebuttal on objective indicia only, I believe, so it would not be directed to these issues.

MR. ABHYANKAR: And that --

THE COURT: No, wait. I limited rebuttal -- so I said there was no rebuttal in this case except for secondary considerations of obviousness?

MS. ANDERSEN: Yes, Your Honor. In the fourth

round.

THE COURT: In the fourth what?

MS. ANDERSEN: The fourth round of testimony.

THE COURT: That's where you're confusing me. Fourth round sounds like it's -- I mean, rebuttal is third round. That's why I'm confused.

MS. ANDERSEN: Sorry Your Honor. Let me be clear. So I'm talking about first round is plaintiffs' infringement. Second round is defendants' response on infringement and invalidity case. Third round is plaintiffs' response on validity. Fourth round Your Honor had limited to rebuttal on objective indicia.

THE COURT: Yes. I'm not sure why I did that. Did I allow for, in the pretrial conference, did I say there would be rebuttal on infringement?

MS. ANDERSEN: No, you did not, Your Honor.

THE COURT: Is there some reason in patent cases that there's not a rebuttal case the way there would be in a normal case?

MS. ANDERSEN: Your Honor, it is very common in my experience in bench trials in pharma cases in Delaware for the judges to request that the defendant sort of pre-rebut.

THE COURT: That's a different question. Sorry. That's just a different question.

I'm just trying to figure out if I'm missing something. I mean, I'm going to let this testimony in just because it's more efficient, but I also want to make sure. You know, I'm trying to figure out why I said what I did. Sometimes I say things that are really not very bright.

I think what I was thinking about was secondary considerations was just I am certainly of the view that, and I've written about this in the one obviousness opinion I spent time on, I mean, I think it's confusing.

I think the Federal Circuit case law, you can read a lot of cases to suggest that you don't get to bring in evidence of secondary considerations until there has been a prima facie case and you get to rebut it. And I have come up with a view that, no, I think you have to permit secondary considerations. It all comes in at once is where I've come out on this. I think that's the better view. I think that's why I may have said what I did, Ms. Andersen.

MS. ANDERSEN: Yes, Your Honor, and we're okay with -- because of the way the rounds are set up, we'll drop our objection.

THE COURT: Okay. I mean, as far as I'm concerned, I didn't know that I ruled out a rebuttal, but I would rather avoid rebuttal. We've got to watch the time. So let's just move forward.

MS. ANDERSEN: Thank you, Your Honor.

BY MR. ABHYANKAR:

Q. **Dr. Donovan, I will restate my question, which is: Are you aware whether Dr. Williams has argued that the '231 describes physicochemical properties of ibrutinib that help fill in the gap, the gaps and guidance to a POSA from the specification?**

A. **Yes, I'm aware that Dr. Williams made those types of statements.**

MR. ABHYANKAR: If we could pull up JTX-11, the '231 patent at column 71.

BY MR. ABHYANKAR:

Q. **Is it your understanding that this is the only physicochemical property that Dr. Williams identified with a patent related to ibrutinib?**

A. **I believe this is the area that he cites. Yes, it's the solubility of form A and form B, the two polymorphic forms, form A.**

THE WITNESS: Form B and the solubility of form A at two pH's, the lower pH, 1, 2, 3 areas for information about solubility in the stomach potentially and then the higher pH's around six or so for information in the gastrointestinal tract. That's how a formulator would use that information and then provides one solubility value for form B at a high pH relative to the pH's in the

gastrointestinal tract. So 7.4.

BY MR. ABHYANKAR:

Q. **Is this information here sufficient to tell or to guide a formulator to practice the full scope of claim 27?**

A. **No, it's not. It isn't telling me anything about the solubility about any of the other forms, the amorphous form to start with, so, no, not enough.**

Q. **And has Dr. Williams identified any specific physicochemical properties other than the aqueous solubility of forms A and B recited anywhere in the '231 patent?**

A. **I believe he has made statements that there are other pieces of information, but they're not in a format useful to a formulator.**

Q. **Let's turn to slide 34, please. No. Go to slide 32, please.**

Are these the purported physicochemical properties of ibrutinib that Dr. Williams pointed to?

A. **Some of them, so he points to or states low bulk density, for example, and there are two densities reported, one for, you know, one for each form and not form A and B and I right now can't remember the forms that are associated. I think it's E and F, and it's a calculated, simulated density calculation that was, that was done based on structure. And there's no information about partition coefficient in the specification.**

And then the aqueous solubility with only for form A and one value for form B.

Q. **And even if a formulator had all of this information and it was disclosed in the '231, would that change your opinion as to whether a POSA, as to whether the '231 patent guides a POSA to fill in the gaps from what is otherwise not disclosed in the specification?**

A. **No. The -- what little information is presented in the specification doesn't provide anywhere, doesn't provide sufficient information to give a formulator the information they actually need to develop or -- to formulate all possible formulations for oral use.**

Q. **And, Dr. Donovan, is there any specific information in the '231 patent that you are aware of that references specifically that ibrutinib suffers from poor bioavailability?**

A. **I don't recall seeing anything in the specification that describes anything about ibrutinib's bioavailability.**

Q. **So let's go to the state of the art, back to slide 36, Mr. Ferrare.**

In your opinion, Dr. Donovan, if you could highlight number 5, please, does the state of the art help fill in the gaps with the lack of guidance in the specification?

A. **No, it doesn't. There isn't any further art about**

ibrutinib in particular than what is in the specification and the rest of the art is not adequate, especially, you know, and you can go back to the art about all of the pharmaceutical formulation, the art about the lubricant and so forth. The state of the art doesn't, doesn't supply the information necessary.

Q. **And is that because the claim covers any oral dosage form?**

A. **That's certainly one of the reasons, that all possible oral dosage forms and the specification doesn't provide the information that a formulator would need to not need to -- to conduct an accepted number of experiments that would actually be able to accomplish the scope of the claim.**

Q. **And if we could go to DTX-2430, please. And, Dr. Donovan, what is this document?**

A. **This is a discovery document that the plaintiffs wrote and presented.**

Q. **And if we could turn to the top of page 42. Plaintiff states here that ibrutinib was a particularly challenging compound to formulate for numerous reasons. For example, ibrutinib is nearly insoluble in water.**

Do you see that?

A. **I see that, yes.**

Q. **And what does plaintiffs' own statement suggest with start of the regard regarding ibrutinib?**

A. **The statement is telling us that the state of the art was that there would be -- the plaintiffs recognize there would be challenges to formulating ibrutinib.**

Q. **Well, let's turn back to slide 36, Mr. Ferrare. If we could next turn to the skill in the art.**

Do you believe that the skill in this particular formulation art is high?

A. **Yes, I do. Even my definition of POSA describes an educational level and experience level that would be considered high.**

Q. **Does that high level of skill in your opinion overcome the challenge and the obstacles that we've seen with respect to the various factors you've analyzed?**

A. **Not, not in light of the breadth of the claim, no.**

Q. **And if we could turn to the predictability or unpredictability of the art, number seven, I think we've touched on this a bit, but briefly, how would you characterize the predictability of the art as relates to claim 27?**

A. **I would characterize it as unpredictable, relatively unpredictable in almost all of the cases. For all possible oral formulations, and when we're dealing with multicomponent mixtures, so the required specific material and the variability among the polymorphs is specific in the dosage forms. It becomes very difficult to predict the**

behavior and the result of formulations in almost all cases.

Q. **And so, finally, if we could turn to the first factor, quantity of experimentation necessary.**

Given your analysis of the factors and the scope of claim 27, how much experimentation would be necessary to practice the full scope of claim 27?

A. **To practice the full scope of the claim, a tremendous amount of experimentation would be necessary because -- I will go back to my introductory slide with all the arrows on it.**

There would be a tremendous amount of iterative processes for each possible dosage form that was going to be formulated at each level of -- with each polymorph of ibrutinib and containing those vast ranges of material that are specified for the formulation. So just a huge amount of experimentation would be required to practice the full scope.

Q. **And I think we touched on this in your background discussion, but do even small changes to a formulation impact the functioning of that formulation?**

A. **Sure, they can, especially, especially small changes in lubricant. It's well-known in the art that small changes in lubricant can cause significant changes in the performance of the formulation.**

Q. **And does the fact that small changes can affect the performance of a formulation also affect the amount of experimentation that's required?**

A. **Yes, sure, because you both need to do a lot of experiments to arrive at the value or values of components in the formulation that you would want, and then you have to understand if you have small variabilities in those, to what extent that's going to impact your final formulation and will it impact the actual therapeutic use or outcome in the intended patient population.**

Q. **So to conclude, Dr. Donovan, what is your opinion on whether or not it would require undue experimentation to practice the full scope of claim 27?**

A. **It's my opinion it would require undue experimentation to practice the full scope.**

Q. **And as a result goes is it your opinion that claim 27 is invalid for lack of enablement?**

A. **Yes. My opinion is that claim 27 is invalid for lack of enablement.**

MR. ABHYANKAR: Thank you, Your Honor. I tender the witness for cross.

THE COURT: All right. Thank you.

Can we hold up, Ms. Andersen?

MS. ANDERSEN: Yes, Your Honor.

THE COURT: Okay. Thank you. Go ahead.

CROSS-EXAMINATION

BY MR. ANDERSEN:

Q. **Good afternoon, Dr. Donovan. I'm Erica Andersen. I will be asking you some questions today.**

A. **Good afternoon.**

Q. **Did you receive a box, maybe a couple boxes of documents that --**

A. **Yes.**

Q. **-- we sent you?**

A. **I received two boxes.**

Q. **Okay. Do you have those with you?**

A. **I do.**

Q. **Okay. Great. And they're open and --**

A. **No, they are not. I was instructed not to open them, so I did not.**

Q. **You can open them now if you wouldn't mind.**

A. **I will step away for just a moment, open both of them and I will be right back with you.**

Q. **Great. Thanks.**

(Pause.)

THE WITNESS: All right. Thank you. I have them opened now.

BY MR. ANDERSEN:

Q. **Great. And, Dr. Donovan, I'd like to turn first to PTX-965, Sandoz's overall quality summary.**

MR. ABHYANKAR: Ms. Andersen -- Your Honor, I'm not sure this document was even cited in Dr. Donovan's report.

THE COURT: And it's cross-examination.

MR. ABHYANKAR: This is a -- this is our -- this is our ANDA, Your Honor, that she didn't analyze. I don't think she has ever seen this document.

THE COURT: Well, so let's wait to see what the question is. I mean, I assume Ms. Andersen is saying, get ready, look at the document. I'm going to start asking. Let's hear what the question is.

BY MR. ANDERSEN:

Q. **And I would like to go to page 80, to the section called '10. What is the rationale for excipient selection? Let me know when you are there.**

A. **So is it page 80 -- never mind.**

THE COURT: Hold up. Ms. Andersen, I mean, I don't think it's appropriate cross-examination just to have a witness read a document. What's the question?

MS. ANDERSEN: The question is: Looking at this section, Sandoz looks at our reference product, they reverse engineered it and they looked at the literature data in order to formulate their product. Correct?

MR. ABHYANKAR: Again, Your Honor, I renew our objection. She hasn't established the witness has ever seen

this document.

THE COURT: Okay. So, look, I think it's an appropriate question if she wants to say, isn't it true that Sandoz was able to formulate or, you know, whatever, Sandoz formulated a drug. That's okay if she knows, if the witness knows.

I am at a loss, though. I mean, I don't understand. I mean, the document is what it document is. If this witness isn't authenticating it, I don't understand why we're having essentially a witness just confirm what's in a document.

MS. ANDERSEN: Yes, Your Honor. The point is, and I will get to that, the specification of the '231 patent is the very source of data that a POSA, that a company like Sandoz could use to formulate.

THE COURT: Okay. Why don't you get to that? Why don't you just go there without having her read a document?

MS. ANDERSEN: Okay.

BY MR. ANDERSEN:

Q. **The specification, Dr. Donovan, of the '231 patent is a source of data a company like Sandoz could look to for information about the reference product; is that correct?**

A. **I -- they could look to the, the '231 for information about the crystal forms of ibrutinib, but there is no**

specific information about what I define as the reference product that I'm aware of that's contained in the '231.

Q. Dr. Donovan, I would like to take a look at your slide DDX-7-9. And there you list pre-formulation testing a POSA would want to perform in order to characterize the active ingredient; is that correct?

A. That's correct, yes.

Q. And i would like to discuss some of the information provided about ibrutinib in the '231 patent specification. Two of the items you have up here is polymorphism and crystallinity?

A. That's correct.

Q. Let's take a look at JTX, column 30, starting at --

THE COURT: JTX what?

MS. ANDERSEN: JTX-11, column 30.

THE COURT: Thank you.

BY MR. ANDERSEN:

Q. And starting at line 44 --

A. And can I ask, do I have a hard copy of the '231 included in any of these materials?

Q. Yes. There should be a copy included in the binder of materials, yes.

A. Can you guide me? I have three binders. Can you guide me what the DTX-number is?

Q. JTX-0011.

MR. ABHYANKAR: Dr. Donovan, maybe tab one.

THE WITNESS: I found it in the cross-examination material. Thank you. Can you tell me what column you highlighted?

BY MR. ANDERSEN:

Q. **Column 30, starting at line 44.**

A. **Okay.**

Q. **And that states, in some embodiments, compound 1 is amorphous and anhydrous; correct?**

A. **That's what this says, yes.**

Q. **And compound 1 is ibrutinib; is that correct?**

A. **That's my understanding, yes.**

Q. **And from column 30 to 36, those columns discuss particular properties of crystalline form A, B, C, D, E and F of ibrutinib; is that correct?**

A. **Well, they describe the -- refresh my memory about these columns. And they're primarily focused on the X-ray diffractograms and IR spectra, and they do have information about from DSC and some about TGA on some of the compounds.**

Q. **Okay. And let's turn to Example 2 in column 66 starting around line 50. That example is entitled X-ray powder diffraction XRPD; is that correct?**

A. **Which lines in column 66?**

Q. **Starting around line 50.**

A. **Okay.**

Q. **Example 2, X-ray powder diffraction.**

A. **Okay.**

Q. **And so the example is entitled X-ray powder diffraction; right, Dr. Donovan?**

A. **It's titled X-ray powder diffraction, yes.**

Q. **And looking at column 66, starting there, you agree that Example 2 provides a protocol for how to determine XRPD patterns performed with ibrutinib; correct?**

A. **Yes, you know, from line 54 to the end of that column, certain it's describing how one would set up the X-ray powder diffractogram.**

Q. **And then continuing on, continuing on in that example in column 67, starting at line 37, there are six XRPD peaks for form A.**

A. **Described, you mean?**

Q. **Yes.**

A. **Yes, that's what's given.**

Q. **And then right under that, line 41 through 42, it states that the crystallinity of form A was unaffected after one week under two different sets of storage conditions.**

Do you see that?

A. **I see that.**

Q. **And then right under that, there are five XRPD peaks for form B; correct?**

A. **Yes.**

Q. **And under that, it says, the crystallinity of form B was unaffected after one week under two different sets of storage conditions; is that correct?**

A. **That's what it says.**

Q. **Column 67 at lines 50 through 55 provides nine XRPD peaks for form C; is that correct?**

A. **Maybe I can't count. No. I seem to be only counting eight.**

Q. **I got nine, but eight or nine peaks for form C?**

A. **I got -- right. I'm sorry.**

Q. **And column 67, lines 56 through 57 states: The crystallinity was unaffected after one week under two different sets of storage conditions?**

A. **That's what it says.**

Q. **If you look at the figures in the patent, XRPD patterns are provided there for forms A through F; is that correct?**

A. **My recollection, let me -- yes.**

Q. **And on your slide -- DDX-7-9, you also identify melting point; is that correct?**

A. **Yes.**

Q. **Let's go to Example 5, column 69 where that example begins. And this example discusses DSC data; is that correct?**

A. **I'm sorry. The sound cut out. What did you say?**

Q. **The example discusses DSC data; correct?**

A. **Yes, it does.**

Q. **And Example 5 reports a peak at about 157 degrees for Form A?**

A. **Yes.**

Q. **And looking at the top of column 70, Example 5 identifies a peak in the DSC at about 115 to 118 degrees for form B?**

A. **Yes.**

Q. **And starting at around line 8 of column 70, a peak in the DSC at about 137 to 139 degrees for form C?**

A. **Yes.**

Q. **And Figure 3 in the patent is the DSC for form A?**

A. **Yes.**

Q. **Figure 7 is the DSC for form B?**

A. **Yes.**

Q. **And Figure 10 is the DSC for form C?**

A. **Yes.**

Q. **And Figure 15 has the DSC for form E?**

A. **Yes.**

Q. **Turning back to your slide DDX7-9, you also identify hygroscopicity?**

A. **Yes, I did.**

Q. **Now, let's turn to Example 6 in the patent, columns 70**

through 71. And that example sets forth parameters for determining hygroscopicity; is that correct?

A. Yes, it does.

Q. And at the bottom of column 70, the patent further reports that form A is not hygroscopic.

A. Under the conditions that were used to measure, yes.

Q. That means form A under those conditions doesn't absorb water; right?

A. As measured, it was not shown -- as measured, it was not deemed to be hygroscopic.

Q. Your slide DTX7-9 also discusses aqueous solubility?

A. Yes.

Q. On direct you said that's a very important property to know; is that correct?

A. Correct.

Q. Turning to example seven in the patent in column 71, that is entitled thermodynamic aqueous solubility?

A. Yes.

Q. It provides an HPLC method for analyzing ibrutinib; correct?

A. Well, I think it provides the HPLC method used for the solubility measurements described in that section, which were for form A and likely used for form B, but I'm not sure that's entirely clear.

Q. And so that HPLC method in example 7 was used to

assess the solubility of ibrutinib for different pHs?

A. **That, that would be what the reader would bring from that information in the column, that HPLC method measures the solubility under the conditions described for --**

Q. **And at the bottom of column 71, it also says that the solubility, it also provides the solubility of form B at a pH of 7.42?**

A. **It states something about the solubility of form B, a pH, yes.**

Q. **Let's turn to example eight at the top of column -- top of column 72. And that example provides a method for determining chemical purity; correct?**

A. **That's what that example states, yes.**

Q. **And chemical purity can be information on stability; is that right?**

A. **I think only indirectly. If you're using the chemical purity assay as your material assay when you are conducting a stability study, I guess it could, but purity and stability are not necessarily -- chemical purity determinations are not always utilized in stability analyses.**

Q. **But you could use it to determine, for example, whether there were degradation products of ibrutinib?**

A. **I don't know actually. I don't know enough about this chemical purity determination to determine whether it was**

able to identify degradant products of ibrutinib or not.

Q. **Your slide DDX-7-9 also lists density; is that correct?**

A. **Yes.**

Q. **And in 2012, a POSA would have been able to perform testing to assess the bulk density of a compound; is that right?**

A. **Yes, they could have.**

Q. **And DDX-7-9 also lists particle size, particle morphology and surface area; is that right?**

A. **That's right.**

Q. **And in 2012, a person of skill would have been able to perform testing to assess those characteristics as well; is that right?**

A. **Potentially. Sometimes it's compound dependent, but, yes, potentially. There were technologies and instrumentation available to the POSA to conduct those experiments.**

Q. **And let's go to your slide DDX-7-13. That's one of your slides entitled formulation design pathway for oral formulation. And here you've highlighted the text; is that correct?**

A. **That's correct.**

Q. **Design and test prototype formulations and modify approach or materials based on results.**

And I would like to go to column 44 of the '231 patent, line 14 through 22. Just let me know when you are there, Dr. Donovan.

A. **I'm there. I'm just reading.**

Q. **And that portion of the patent provides the manufacturing techniques; correct?**

A. **They may be used as manufacturing techniques. They may just be used as preparation techniques, but they're, they're a method that are used to treat material in pharmaceutical preparations.**

Q. **I'd like to turn to Example 12 now, which starts at column 74, line 55.**

Example 12 is entitled, safety and tolerability study of compound 1 in chronic lymphocytic leukemia.

Do you see that?

A. **I see that.**

Q. **It provides a clinical study for all humans using an orally administered dose of 420 milligrams; correct?**

A. **It provides a protocol. It provides no information about whether that study was ever conducted or what the results were.**

Q. **And I'd like to turn to example 13 in example 75, and that's entitled, safety and efficacy of compound 1 in subjects with relapsed refractory mantle cell lymphoma.**

Do you see that?

A. **Yes.**

Q. **And Example 13 as well provides a clinical study for in humans using a 560 milligram dose of ibrutinib administered in multiple capsules; is that correct?**

A. **Can you point out what line it describes multiple capsules?**

Q. **Compound 1, line 53. Compound 1, 560 milligrams a day in the form of capsules.**

A. **Okay. I'm not sure that that tells me that it's in multiple capsules.**

Q. **But capsules were administered in Example 13?**

A. **It was administered in the form of capsules, yes.**

Q. **And finally, let's go to example 14 entitled Phase 2 study of combination of compound 1 and rituximab in high risk chronic lymphocytic leukemia and small lymphocytic lymphoma patients.**

Example 14 provides a Phase 2 study using an orally administered dose of three times 140 milligrams of ibrutinib capsules. You see that?

A. **I do see that. Yes, again. It is the first conducted and data being obtained.**

Q. **You looked at Example 11 in the '231 patent in your direct; correct? I believe that's Table 6.**

A. **Yes.**

Q. **And in your opening report, you called Example 11 a**

working example.

Do you recall that?

A. **Not specifically.**

Q. **Okay. If we could go to your opening report at paragraph 29, please. And I believe you should have a binder with your report, Dr. Donovan, but we'll bring that up as well. 29.**

A. **Okay. Which report is it that we're looking at?**

Q. **Your opening report?**

A. **Okay. What page?**

Q. **Paragraph 29. 29. Yes.**

A. **Okay. So I see on the screen as what I've seen in the hard copy. I'm in the same place.**

Q. **And you called Example 11 a working example of the patent; is that correct?**

A. **I called them working examples that were given in the patent, but they might not meet the, all of the description of claim 27.**

Q. **But a person of skill would look to the entire specification, including the working example of Example 11; right?**

A. **Well, they, they would -- they would see that in the, in the specification, certainly.**

Q. **And Example 11 contains .25, 2.5 percent as a range of magnesium stearate as a lubricant; is that correct?**

A. **It's describing the level of magnesium stearate in that general tablet formulation between .25 and 2.5 percent, yes.**

Q. **And you testified on direct that 15 percent of lubricant could cause issues with the formulations; is that correct?**

A. **Yes. 15 percent of lubricant, you're going to have characteristics of the lubricant now giving characteristics to your final dosage form and those could be negative.**

Q. **And a POSA would have understood that in 2012; is that correct?**

A. **A POSA was aware of issues caused by lubricants in particular and other formulation components in 2012.**

Q. **And a POSA would have known that if too high of an amount of lubricant is used, the formulation could fail; right?**

A. **They would be aware that there have been manufacturing and performance problems with high levels of lubricant. Specific materials have specific properties and too much of them in a formulation may lead to negative performance attributes.**

Q. **You looked at the Handbook of Pharmaceutical Excipients and specifically the magnesium stearate portion, the portion that stated the lowest possible concentration should be used.**

Do you recall that?

A. **I recall that, yes.**

Q. **And a POSA would have known that as well in 2012; is that right?**

A. **That was known to POSAs in 2012, yes.**

Q. **And a POSA in 2012 similarly would have understood that effective lubrication could result in waterproofing of tablets or delayed dissolution of the drug substance; right?**

A. **That had been reported in other formulations, yes.**

Q. **I'd like to turn to DTX-2223, pharmaceutical pre-formulation and formulation, Dr. Donovan, which is a document you cited in your reply report; is that correct?**

A. **Yes, it is.**

Q. **And this is a book that a person of skill would have had available in June of 2012?**

A. **I believe the copyright that we infringe on this is about 2002, so, yes, this would have been available to a POSA.**

Q. **Let's turn to page 413 of this reference. And I would like to look at table 11.9. This is a list of lubricants and their uses.**

Do you see that?

A. **I see that.**

Q. **Polyethylene glycol, 4,000 and 6,000 are listed.**

A. **Mm-hmm.**

Q. **And the level required listed as two to ten percent?**

A. **I see that.**

Q. **And looking in the '231 patent, JTX-11, column 5, starting at line 63 and going over to column 36, that's the list of different lubricants in the patent you looked at on direct; right?**

Column 45, please. 45. No worries. Starting at line 63 and over to the top of 46.

And that's the list of lubricants you looked at on direct; right, Dr. Donovan?

A. **It is, yes.**

Q. **And polyethylene glycol 4,000 and 6,000 are listed in the patent as well; right?**

A. **Yes, they are.**

Q. **I want to look back at the table on 413 of DTX (inaudible). There we go. And there stearic acid is also listed; is that correct?**

A. **Yes.**

Q. **And the level required is .25 to 2 percent; is that right?**

A. **That's what's reported in the table.**

Q. **And if we could look back at the list of lubricants in the '231 patent, stearic acid is also listed as a lubricant; is that right?**

A. **Yes.**

Q. **And turning back again to the table on 413, sodium sterile fumarate is also listed?**

A. **It's listed in the table, yes.**

Q. **And that's a lubricant used by Sandoz?**

A. **I don't know.**

Q. **And the level required column is .5, 2 percent?**

A. **That's what the table says.**

Q. **And looking at the '231 patent, at the bottom of 45, sodium sterile fumarate is listed in the patent as suitable lubricant as well?**

A. **Yes, it is.**

Q. **I'd like to go to your slide DDX-7-25, please. And there you indicated that claim 27 provides a range of ibrutinib and the excipients; right?**

A. **A range of the amount in the formulation and the excipients?**

Q. **Yes.**

A. **Yes.**

Q. **Including a 40 to 50 percent weight by weight range of ibrutinib?**

A. **Yes. From claim 27, yes.**

Q. **And it was your testimony these ranges are broad; is that right?**

A. **Yes.**

Q. **I want to take a step back and I want to talk about drug content for a moment.**

Even for an approved drug product, some variability in the amount of ingredient in each dosage form is allowed; correct?

A. **Typically, yes.**

Q. **For example, not every 140-milligram capsule made by Sandoz is going to have exactly 140 milligrams of ibrutinib; right?**

A. **That's the usual understanding, yes.**

Q. **And drug companies typically provide specification for drug content uniformity to the FDA; is that right?**

A. **Yes.**

Q. **And they provide specifications for drug assay at the FDA?**

A. **What do you mean by drug assay?**

Q. **Drug uniformity assays to the FDA.**

A. **Can you -- can you be more specific about that?**

Q. **Looking at the content of drug uniformity in the product.**

A. **I still don't understand what you're asking me --**

Q. **Sure.**

A. **What information is provided to the FDA.**

Q. **So companies provide information on drug content uniformity specifications to FDA; correct?**

A. **They do.**
Q. **And those specifications can vary by as much as ten percent; right?**
A. **It depends.**
Q. **But they can vary by as much as ten percent; is that right?**
A. **Under the, under the general USP chapter on content uniformity, I suspect that it's about ten percent. I don't remember the exact numbers.**
Q. **Okay. I want to talk about what that means practically if it's about ten percent.**

So let's say I have a formulation that's supposed to have about 45 percent weight by weight of ibrutinib. Okay?

A. **Okay.**
Q. **And an assay measure that only reported 90 percent of that 45 percent would still fall within the specification; right?**
A. **It may. I don't know what the specification is, but if we're going to do plus or minus ten percent --**
Q. **And similarly, if you have a ten percent tolerance, you could have up to 110 percent of that 45 percent and still fall within the specification?**
A. **For the drug content, yes.**
Q. **Correct. So, in other words, if you did the math, the**

assay could report as low as 41.5 percent of ibrutinib and as high as 49.5 percent of ibrutinib and still be within the specification; is that right?

A. **I need to do the math, but what you have said strikes me as being correct, yes.**

Q. **And that would be the range that is tolerated for a single formulation; is that correct?**

A. **Not necessarily, because what is being described in claim 27 and the amount, there's a situation where the amount of ibrutinib measured in the tablet or whatever tablet, a fine dosage form to think about, that the whole tablet weight was lower by ten percent. All the other components were there, present in the correct proportion, it's just the entire tablet weight was low.**

Those content uniformity tests don't say anything about the content, directly say anything exactly about the content ratio of each of the components unless you actually measure each of the components.

Q. **Right. But the ultimate amount of ibrutinib could be as high as 49.5 percent and still be in the specification?**

A. **I -- I'm not sure I know that I could agree with that.**

Q. **Okay.**

A. **Because that would require me to assume that there**

was, you know, some other combinations were too low by ten percent and I'm not as familiar with that situation occurring in manufacturing and testing.

Q. **Okay. But if you had 110 percent drug content uniformity specification, you could have an overage of up to ten percent of active ingredient and still be within the specification; is that right?**

A. **What do you mean by overage?**

Q. **The highest end of the range. If you have a dose content uniformity specification that varies from 90 to 110 percent of the amount, then you could have a tolerance up to 110 percent of the active ingredient and still be within the specification.**

A. **Under some circumstances, that could be the case.**

Q. **You talked about a number of different oral dosage forms in your direct.**

A. **Yes.**

Q. **And I would like to look at your slide DDX7-22, and there you state that the claims cover any oral dosage form.**

Do you see that?

A. **Yes.**

Q. **When we look at claim 27, the claim requires microcrystalline cellulose, croscarmellose sodium, sodium lauryl sulfate and a lubricant.**

A. **Yes, or a combination potentially.**
Q. **And it's your opinion that the combination of microcrystalline cellulose, croscarmellose sodium, sodium lauryl sulfate and a lubricant like magnesium stearate are standard terms for solid oral formulations in particular?**
A. **Those materials get used in a lot of formulations intended for administration at a variety of sites, and so the -- I don't agree in particular. They are certainly used in oral pharmaceutical formulations, but they are also used in many other pharmaceutical formulations.**
Q. **And, Doctor, you were deposed in this case?**
A. **Yes, I was.**
Q. **And you gave truthful testimony at that deposition?**
A. **Yes, I did.**
Q. **And I'd like to pull up your transcript, 118:16 through 119:6.**

MS. ANDERSEN: And I believe the deposition transcript should be in her binder as well.

THE WITNESS: Do you know the DTX number?

MS. ANDERSEN: It should just be in your binder with expert reports and have your transcript.

THE COURT: So can I -- this is not the first time this has happened. I'm not used to the way folks, some of the folks are referring to deposition transcripts.

You've got -- what's the pending question?

MS. ANDERSEN: The pending question was: It's your opinion the combination of microcrystalline cellulose, croscarmellose sodium, sodium lauryl sulfate and a lubricant like magnesium stearate are standard materials for solid oral dosage forms in particular.

THE COURT: Okay. She answered the question. All right. And then you say, you were deposed in this case.

Are you suggesting that the answer to the question is inconsistent with what she testified at her deposition?

MS. ANDERSEN: Yes. She just said she wouldn't call them standard and at her deposition she said these are standard materials for solid formulations in particular.

THE COURT: Okay. So why don't you just ask her. She said here, what she said is, these materials get used in a lot of formulations. I don't agree in particular. They're certainly used.

So then why didn't you say, didn't you testify that they were standard when you testified in your deposition and she what she said? I mean, I guess is that what we're getting at?

MS. ANDERSEN: That's what we're getting at.

THE COURT: Let's do it that way. We'll save everybody a lot of time if that's how we do these instead of

going through the exercise of reading depositions.

THE WITNESS: Thank you, Your Honor.

MS. ANDERSEN: Yes. Of course, Your Honor. I would like to go to DDX-261 --

THE COURT: Ms. Andersen, I'm not saying you should abandon this. She might just admit that she said something different in her deposition and maybe she won't. If she won't, then you can confront her with her deposition.

I'm not telling you to move on. It's just confusing to me what -- I'm not even sure her answer is exactly inconsistent with what she said, so why don't you just ask her.

BY MR. ANDERSEN:

Q. **Dr. Donovan, at your deposition you testified that solid formulations in particular contain combinations of microcrystalline cellulose, croscarmellose sodium, sodium lauryl sulfate and magnesium stearate; is that correct?**

A. **In the context of that portion of my deposition, yes, that those combinations are seen in topical oral dosage forms. Those materials are also seen in many other dosage forms designed for administration at other relative administrations.**

Q. **I'd like to go to DTX-2261, the Handbook of Pharmaceutical Excipients. And you talked about the handbook on direct; is that correct, Dr. Donovan?**

A. **Yes, I did.**

Q. **And a person of skill would have had access to the handbook in 2012; is that right?**

A. **Yes, they do.**

Q. **I would like to turn to page 129 and this is the monograph for crystalline -- microcrystalline cellulose; correct?**

A. **That's what it looks like on the screen. Do I have a hard copy of that?**

Q. **I think it's in your direct binder, Dr. Donovan?**

A. **I've got to get my direct binder then.**

Q. **And let me know when you are there.**

A. **My direct binder, I can find the monograph for magnesium stearate, but not the monograph for microcrystalline cellulose. Are you sure it's in my binder?**

Q. **It should be. We have it on the screen if it's not, if it's not there.**

A. **Okay. Well, I will use the screen version because I don't find it in my materials.**

Q. **Thank you.**

So if you turn to section seven of the microcrystalline cellulose, applications in pharmaceutical formulation of technology?

A. **Yes, okay.**

Q. **It states, microcrystalline cellulose is widely used in pharmaceuticals primarily as a binder/diluent in oral tablet and capsule formulation.**

Do you see that?

A. **I see that.**

Q. **And that is something a POSA would have known in 2012?**

A. **A POSA would have understood that microcrystalline cellulose is used in oral tablet and capsule formulations, yes.**

Q. **Okay. And I'd like to look at the monograph for croscarmellose sodium, please.**

A. **Okay. I'm going to ask you in my answer that regardless of what the monograph literally states, microcrystalline cellulose is in plenty of other dosage forms, nasal spray dosage forms in particular that I'm most familiar with.**

Q. **But to be clear, Dr. Donovan, this portion, the applications in pharmaceutical formulations in technology says microcrystalline cellulose is widely used in pharmaceuticals primarily as a binder/diluent in oral tablet and capsule formulations; right?**

A. **That's the way the author chose to write that. It's used in a lot of pharmaceutical formulations.**

Q. **I'd like to look at page 206. I apologize if you**

don't have it. We thought you did. That's on the screen. That's the monograph for croscarmellose sodium?

A. **Can the person in charge of video increase the size of that because I'm reading on a small screen.**

Q. **And can you see that, Dr. Donovan?**

A. **Yes, thank you.**

Q. **And, again, looking at section seven, applications in pharmaceutical formulation or technology states, croscarmellose sodium is used in oral pharmaceutical formulations as a disintegrant for capsules, tablets, and granules.**

Do you see that?

A. **Yes. That's telling us how it's used in oral pharmaceutical formulations.**

Q. **And that's something that a POSA would have known in 2012; right?**

A. **Yes. It can be used in oral pharmaceutical formulations as a disintegrant in capsule, tablets and granules. It can be used in other formulations also.**

Q. **But the reference provides that it's used specifically in capsules, tablets and granules; is that right?**

A. **No, it doesn't provide that specifically. It just says, in oral formulations, it's used as a disintegrant.**

Q. **In oral formulations?**

A. **Well, it's used in oral formulations as a**

disintegrant.

Q. **And continuing with disintegrants, I'd like to look back at the '231 patent, JTX-11, column 44, line 63 through 65.**

And this passage provides that disintegrants help rupturing the dosage form matrix by swelling or capillary action when moisture is absorbed into the dosage form.

Do you see that?

A. **I see that.**

Q. **And not all oral dosage forms are going to require rupturing the dosage form matrix by swelling or capillary action when moisture is absorbed; right?**

A. **Can you repeat that again.**

Q. **Not all oral dosage forms are going to require rupturing the dosage form matrix by swelling or capillary action when moisture is absorbed into the dosage form; right?**

A. **They might not require that and that characteristic might be -- you know, it's a matter of the amount of croscarmellose that's included, exactly how much swelling and how much, whether we get to rupturing or not occurs.**

Q. **For example, a solution wouldn't require rupturing the dosage form matrix by swelling or capillary action when moisture is absorbed into it; right?**

A. **In its final composition as the solution, all of the material in solution, no, it won't require that, but during production or something, I don't know. There's nothing to tell me that -- stuff like that might not have occurred.**

Q. **Right. But as a final solution, you agree it would not occur?**

A. **The disintegration action wouldn't occur, but the substance that could act as a disintegrant might still be in the solution.**

Q. **But the disintegrating action would not occur; is that correct?**

A. **In the final composition in its final state, the disintegrant would no longer be acting to rupture the material, but it may have acted in the manufacturing or formulation stage.**

Q. **Turning from disintegrants to lubricants, you agree that lubricants typically help with the handling and manufacturing of the composition by reducing frictional forces between formulation components and contact surfaces of manufacturing equipment; right?**

A. **In general, that's their most, that is their typical primary purpose, yes.**

THE COURT: Hold on. I'm sorry, Ms. Andersen. I think Mr. Abhyankar is standing up. Hold on. Let me

switch my screen here.

Is there an objection? You're standing?

MR. ABHYANKAR: Oh, no. I don't have an objection, Judge Connolly. I'm just standing here watching.

THE COURT: You just popped up on my screen.

All right. Sorry, Ms. Andersen. I disrupted your flow. Sorry.

MS. ANDERSEN: Not a problem, Your Honor.

BY MR. ANDERSEN:

Q. **And you would agree, Dr. Donovan, that frictional physical forces between formulation components and contact surfaces of manufacturing equipment are common for capsules and tablets; right?**

A. **In particular, on most of the high speed manufacturing equipment, yes.**

MS. ANDERSEN: I have no further questions at this time.

THE COURT: All right. Thank you, Ms. Andersen.

All right, Mr. Abhyankar, do you have any followup, redirect?

MR. ABHYANKAR: Just a few questions. Can we have a five-minute break, Your Honor, if that's okay?

THE COURT: Well, if you have a few questions, why don't we finish it out?

MR. ABHYANKAR: Fair enough.

THE COURT: Dr. Donovan, you're good to go for a couple more minutes?

THE WITNESS: Yes. I'm fine, Your Honor. Thank you.

THE COURT: All right. Let's go ahead.

MR. ABHYANKAR: Could you pull up JTX-11, column 3, beginning at line 62, column 4. Column 3. Column 3. I think it was line 62, column 4, line 25.

REDIRECT EXAMINATION

BY MR. ABHYANKAR:

Q. **Dr. Donovan, do you recall Ms. Andersen directed you to these portions or this portion of the specification regarding the crystalline forms of ibrutinib described in the '231?**

A. **Yes, I remember.**

Q. **Are these properties listed here, are those properties of the crystalline form that a formulator is focused on typically when designing a formulation?**

A. **No, not typically. The formulator anticipates that the material that they have been given as the active substance to formulate has been characterized somehow and that there may be reasons during formulation to then use X-ray powder diffraction to then evaluate the crystal form of the material, but having the X-ray powder diffraction parameters themselves as a guide, the crystal structure**

itself is not typically a useful -- you know, the 2-Theta angles and so forth don't directly tell a formulator about compatibility with other materials or much of anything else really about the substance. But it's certainly important as far as assuring and being able to test that you still have the crystal form at the end of your formulation and manufacturing process.

Q. **Got it. And Dr. Williams did not point to any of these properties, you know, for purposes of his opinions regarding the '231 patent; is that right?**

A. **Not that I recall.**

Q. **And to confirm, the only aqueous solubility information as disclosed in the '231 patent are forms A and B?**

A. **That is what I have found, that there's pH dependent solubility information on form A and one solubility measure for form B.**

Q. **And I think, I think you testified about this earlier with Ms. Andersen, but is aqueous solubility one of the more important physicochemical properties a formulator would look at when designing formulation?**

A. **It's certainly a very important property because just on a general basis, I have to be able to understand how or project how the total dose that was administered is going to go into solution at the site I'm going to administer at and**

it doesn't necessarily have to do that all of the time, but I need an environment where it's possible to have that happen and so I need to know about the solubility even to begin to identify an appropriate dosage form and then knowing about the solubility tells me things about how that drug substance may likely be absorbed or conditions I need to try to put it into to have it.

Q. **And do you recall your question with Ms. Anderson regarding using an amount of lubricant up to 15 percent formulation?**

A. **Somewhat vaguely.**

Q. **In your opinion, would a POSA know what the dividing lines would be between the amount of lubricant that would work in a formulation versus the amount of lubricant that wouldn't?**

A. **No, because formulations are multicomponent mixtures with material that performs multiple functions. So just knowing a value, no, they wouldn't know.**

Q. **And if I could have Mr. Ferrare pull up slide, I think it's 26, please. And just to confirm, is claim 27 limited to a capsule?**

A. **No. Claim 27 allows for any pharmaceutical formulation for oral administration.**

Q. **And it's not limited to a tablet?**

A. **No. It's limited to the formulations that we could**

deliver orally.

Q. A continued oral dosage form? In your, any oral dosage form?

THE COURT: Just to be clear, Dr. Donovan, are you sure it's any oral dosage form?

THE WITNESS: Well --

THE COURT: I'm saying that facetiously. I think we've established it three times. Okay? All right. We're good. Thank you very much for your testimony.

MR. ABHYANKAR: All right. Thank you.

(Witness excused.)

THE COURT: All right. We could take a break now. What's going to be next?

MR. ABHYANKAR: I believe we have more deposition testimony for Your Honor from one of the inventors on the '231 patent and as well as the -- actually, the main inventor on the '548 as well.

THE COURT: And how long is that going to be?

MR. ABHYANKAR: I believe it's around 30 minutes. Is that right? Forty, 40 minutes.

THE COURT: Then what's after that?

MR. GUTMAN: The direct examination of Dr. Fassihi for the Alvogen matter.

THE COURT: We'll take a ten-minute break. When we come back at 3:00, each side be ready to have a lawyer

talk about the significance of the testimony we've just heard for the last couple hours to answer some questions I might have about enablement law and written description law. Okay? It won't be long, but just designate somebody, please.

All right. I will talk to you at 3:00. Thanks.

(Short recess taken.)

- - -

(Proceedings resumed after the short recess.)

THE COURT: All right. So let's see. Here are my questions. I'm trying to understand just as a matter of law. I never had a written description or enablement case.

So does everyone agree that the written description must convey that the inventors were in possession of the full scope of the invention at the filing date?

Ms. Andersen, alphabetical order, you're first.

MS. ANDERSEN: I think the full scope language really comes from enablement law, not written description. Certainly, it has to describe the invention, show the inventors we're in possession of it, but the full scope language I think really comes from enablement.

THE COURT: Frankly, that's the language that's hanging me up and I wanted to talk about it.

So the bottom line is you're saying you don't

agree, that that is not a fair statement of the law, that it's overstating it for written description?

MS. ANDERSEN: I think that to the extent they are saying that every single possible conceivable formulation has to be described in the patent, which is what the full scope sounds like, that is certainly not the law.

THE COURT: Okay. Ms. Clayton, it was your slide.

MS. CLAYTON: Yes. Your Honor, I do believe that's the language that is used. I don't -- I don't disagree that, you know, if you were to do a combination permutation calculation of that claim, you would come up with, I don't know, tens of thousands of formulations. Not every single formulation would have to be explicitly set forth, but you do have to at least set forth, for example, the ranges, right, of the lubricant that you are claiming. And here they have not even come close to setting forth that particular range.

THE COURT: All right. Well, let me stop you there.

So for starters, are you telling me that at some point you're going to show me a case which is going to say point blank that for the written description to pass muster, it must convey that the inventors were in possession of the full scope. There's going to be some case law that says it

has to be the full scope of the invention?

MS. CLAYTON: Yes, I believe that's true, Your Honor. I think I can have a cite for you in just a moment.

THE COURT: Okay. All right. But even you as you acknowledge, let's assume some of the case law says that. I mean, it strikes me, I also know there are cases out there that say, hey, ranges are permissible. Right? You can have a range.

MS. CLAYTON: Right. We don't disagree with that.

THE COURT: At some point, to Ms. Anderson's point, if you have a range, you have an infinite number of points within the range. Right? You agree with that? It can't just be the law that you have to prove every single -- that just wouldn't make sense. The law can't be that. But, on the other hand, I'm inferring from something you said, that you are going to take the position, and I guess the question is: Does the case law support this, that you do have to at least in the written description convey both ends of the range that's claimed.

Is that your position?

MS. CLAYTON: That is certainly our position. Yes, Your Honor.

THE COURT: And you think there's case law out there that says that? The minimum and the maximum of the

claims range has to be taught or conveyed in the written description?

MS. CLAYTON: I don't know if it specifically talks about ranges, about the language that's used, but I do believe there is case law that supports that general proposition.

THE COURT: Ms. Andersen, what's your reaction to that?

MS. ANDERSEN: My reaction is that this shows possession commensurate with the scope. It doesn't require what Ms. Clayton is suggesting. I mean, the Ariad cases said you don't even need an example to have written description, so I don't think it's the case that, you know, you have to show both ends of the range of some working example. You just have to show possession of, that the inventors possessed formulations commensurate with the claim and I think we have done that. We've shown our working examples and that a POSA could work from them. We've also shown there are a lot of properties of the active compound and so I don't agree with what Ms. Clayton is saying.

THE COURT: Mr. Gutman, do you have anything to add?

MR. GUTMAN: I do, Your Honor. With respect to ranges, I think I can clarify that issue.

You don't need to -- in order to claim a range,

a range is defined by the endpoint, and so you really have to have possession of the defined range, which means in the specification, you must say that the range is set out with these end points.

So you can't say, like, let's say there's a range 1 to 100, but you set out in the, in the specification 5 to 23. You can't claim a range of 1 to 100 if you don't have a description in your specification that defines the claimed range.

THE COURT: All right. I get it. You and Ms. Clayton are on the same page. This is going to be a legal question. But I will tell you what I will do is, I don't want briefs, but if anybody wants to get me, you know, Monday or Tuesday, like, the best case or two that you think supports these two different positions, because I think I understand the positions, and I will take a case. You can do a cover letter that says, hey, here are the cases that we think best address the issue of what is required to establish the full scope of the invention for the written description requirement. Okay? All right.

MR. GUTMAN: Your Honor --

THE COURT: Yes?

MR. GUTMAN: May I just address the second point very briefly about possession of a genus?

THE COURT: I didn't ask --

MR. GUTMAN: The full scope, the full scope of the claim, what that means in the context of written description law.

THE COURT: Well, I think I kind of asked for that. For me, I just want this, this is what I'm looking for. Do you want to show me the range? I don't want to get into this genus thing. I think that's a bigger question and we've got to tackle that before lunch. And I just think we'll never finish this evening. So let's save that. I'm going to come back to that incidentally. I think that's a huge issue.

So I've got a quick question for you all. There was some testimony in the depositions this morning that refer to crystal structure. I'm going to assume crystal and crystalline are synonymous when we're talking about crystal structure and crystalline structure.

Do you agree, Mr. Gutman?

MR. GUTMAN: Yes Your Honor. A crystal is crystalline.

THE COURT: Do you agree, Ms. Clayton?

MS. CLAYTON: Yes, I agree, Your Honor.

THE COURT: Mr. Sipes, do you agree?

MR. SIPES: For purposes of this case, if you want to hear to something referred to as crystalline ibrutinib, it's means it's in a crystal form. That's

correct.

THE COURT: There was deposition testimony from the inventors. They start talking about crystal structure and nobody said anything about it. I'm just assuming that is the exact same thing as crystalline structure.

MR. SIPES: Without having it right in front of me, I believe that would be the case. I've hate to speak for the inventors without having the exact passage in front of me, but I believe that would be the case.

THE COURT: Okay. All right. Then last thing, I'm going to let you, both sides, submit cases. And I'm not looking for argument and I won't read argument. Here's what I'm inviting a submission of cases for. And basically, it's this. Is a POSA precluded from considering information that was disclosed in a patent application or patent that should not have been disclosed in that application or patent under the applicable regulations that govern patent applications and patents in the PTO? All right? Does that make sense? You are looking a little perplexed, Mr. Sipes.

MR. SIPES: I will confess I'm not quite sure what it's germane to.

THE COURT: Well, here's what it's germane to. I thought you would know exactly what it's germane to.

I've got an expert witness who says even though he's not a lawyer, he's a POSA, he's a scientist, he

wouldn't look at an international patent that's referenced by incorporation because he has got a slide that tells him some patent regulation says it shouldn't have been in that application.

And when I heard this, as you can probably tell from my questioning of him, I thought that sounded -- it was incredible to me that a POSA would be precluded from looking at what is in a public document.

And so like I'm thinking to myself, so if the Patent Examiner made a mistake and allowed something to be put publicly in a patent, I'm going to be shocked if the case law says that we should go back and pretend it was not disclosed in the patent, and a POSA wouldn't have considered it.

But maybe Alvogen has a different view. I mean, I think they must have a different view, so I don't want argument on it, but what I want is case law. Not that I expect anybody to be able to find a case, but if there's a case out there that says somehow we're supposed to pretend that it doesn't exist in the mind of a POSA in a public document because apparently it didn't comport with. And it's not clear to me it did not comport with the disclosure of the IPO, but putting that aside for the moment, we'll get that in post-trial briefing perhaps. Let's at least follow through on that.

So does everybody understand the mission if you have a case? Mr. Gutman, you are the one I think that's actually going to have to come up with a case that says this.

Do you understand the question?

MR. GUTMAN: I believe so, Your Honor.

THE COURT: Okay.

MR. SIPES: Your Honor, and we will do our best to find cases that address -- you know, our position is they were not forbidden from using the priority application to address the -- but I understand the question.

THE COURT: Yes. It's just hard for me to think, you could probably come up with a hypo, something. Maybe there's a case that some trade secret was disclosed publicly and should that be considered by a POSA, you know, something like that.

MR. SIPES: I understand. We will, we will look for something.

THE COURT: Okay.

MR. SIPES: Your Honor, as well as long as we're making case law submissions, if we find a case addressing a genus of crystalline form, we will submit that as well. If we find a case.

THE COURT: Mr. Gutman should have and Ms. Clayton as well. I mean, yes. I mean, I'm not looking for

briefing, but I'll saying if you find a good case, that you say, hey, this might help me as I listen to the rest of the evidence, yes, that's fine.

MR. SIPES: We will look for that, Your Honor.

THE COURT: All right. That goes for everybody. Okay.

MS. CLAYTON: Your Honor, just to be clear, you did mention enablement, but on enablement, you would be interested in that type of case law? We believe we have a case that's literally on all fours with the '231 patent.

THE COURT: Here's the thing. I notice Ms. Andersen, you know, I opened up by saying I had some questions on written description, enablement, and I asked did anybody disagree with your slide definition of written description and what Ms. Andersen said was, full scope she thought really was enablement law, not written description law, and so because of that, I thought, it sounds like, and I thought let's tackle this written description thing first.

MR. SIPES: We can submit cases on enablement, too, Your Honor, just so that you have it.

THE COURT: That's fine. Mr. Gutman, Ms. Clayton, go ahead. You guys can do the same thing.

MS. CLAYTON: You just want the cases, nothing else, just the cases that you think are best for

the issues?

THE COURT: When say issues, I was really trying to narrow the issues.

MS. CLAYTON: Yes. Written description and enablement with respect to Sandoz and I guess there's another issue with respect to Alvogen.

THE COURT: Right. But keep in mind, it's not just with respect -- it's not like your entire case.

MS. CLAYTON: Understood, Your Honor.

THE COURT: All right. So then here is the last thing I'm going to do and I know it's a lot of work, but you know what, I'm going to have to work all weekend. So what I'm going to allow you to do is this. With the claims that have been put in issue to date for both infringement and invalidity, I'm going to let you, the three of you submit to me on Monday essentially a decision tree and it's going to be, you know, you take the claim and for infringement or validity. You just, you say, here are the questions and in the order I should answer them. All right? That if you were me, if you were making -- I don't want you to provide substantive answers. I just want you to ask the questions. And, you know, so the question, let's say, number one, you know, did Alvogen infringe, you know, whatever claim -- I'm sorry, they are all jumbled in my head right now.

I don't mean I want the law. What I mean is I

want specifically, you know, did Alvogen do this? I would like you to narrow. I would be very intrigued by the three of you for every claim when it comes to infringement or invalidity that's at issue giving me the order of the specific question I ought to ask.

Again, if you start just quoting me from the law and all of that, I probably won't even read it. I am looking for the specific, hey, here's what you'd better focus on to answer this question.

Does that make sense?

MS. CLAYTON: Yes, Your Honor.

MR. SIPES: It does Your Honor. You may know from my opening, I like decision trees. We'll put them together.

THE COURT: Thank you, all. Any other questions on that, Mr. Gutman? Do you have a question?

MR. GUTMAN: No. I understand your last point, Your Honor. One thing that I wanted to suggest because most of the issues that are being submitted to Your Honor are with respect to questions that you had concerning, for example, Sandoz's patents at issue, you had raised some questions yesterday regarding inherency. I mean, we can submit cases to you that answer some of your questions regarding inherency because I think that would be of value in considering the issues pertaining to the '455

patent as opposed to the '548 patent, which only applies to Sandoz.

THE COURT: But I thought you basically -- I thought the plaintiffs backed off on that position about inherency, whether I should consider the ANDA.

I thought --

MR. GUTMAN: Oh, yes. No. I was talking more -- I apologize, Your Honor. I was speaking more to Your Honor's questions regarding what is the law of inherency with respect to anticipation.

You seem to --

THE COURT: Inherency and anticipation. Oh, I see. No briefing, but if you have a good case that you think really explains -- the issue I was grappling with is, you know, basically, it just seems to me there's at least some intersection of the idea of inherent anticipation with obviousness and trying to figure out how do you -- how do you distinguish between those two. If you've got a case that helpfully discusses that, I will read that case.

I don't want to read just kind of cases generally about anticipation and that kind of thing. All right.

MR. GUTMAN: I understand, Your Honor.

THE COURT: All right. Thanks. All right. Thank you, all.

MR. SIPES: Thank you.

THE COURT: Let's go forward.

MS. CLAYTON: Your Honor, at this time we're going to introduce the deposition testimony of Mr. Norbert Purro. He is one of the named inventors on both the '548 and '231 patents as well as the '455 patent.

Mr. Purro is a former employee of Pharmacyclics and was one of their 30(b)(6) witnesses. He was deposed by the defendants on November 12th, 2019.

You will hear 46 minutes and 26 seconds of testimony. Twenty-three minutes and 10 seconds will be charged to defendants and 23 minutes and 16 seconds will be charged to plaintiffs.

THE COURT: All right. Thank you.

(The videotaped deposition of Norbert Purro was played as follows.)

"Question: Thank you, Mr. Purro. Good morning. Could you please state your full name and address for the record?

"Answer: My full name is Norbert Maximilian Purro. I live at 15460 Corrine Drive in Los Gatos, California. Zip, 95032.

"Question: Mr. Purro, let's just go through your background. Can you tell me about your educational background? Did you get an undergraduate degree?

"Answer: I have an undergraduate degree from Switzerland where I went to school. I graduated in 1979, which is what -- what would be roughly equivalent to a bachelor's degree in the U.S.

"Question: What degree did you graduate with?

"Answer: Chemistry.

"Question: Any particular discipline or just chemistry generally?

"Answer: I did a -- I also studied pharmaceutical sciences, which is called ganik in German.

"Question: Sorry, sir. Could you say that again?

"Answer: Ganik, G-A-N-I-K.

"Question: And did you receive a degree in pharmaceutical sciences?

"Answer: I got a certificate for finishing my school as a chemist.

"Question: Did you have any experience working with pharmaceutical formulations as part of your course work?

"Answer: Yes, I did.

"Question: Okay. Can you provide some background on with a types of --

"Answer: The way my schooling was structured, that I was actually working for Ciba-Geigy as I was

attending school and I was doing intern work at Ciba-Geigy for three years at different disciplines. One was solid oral dosage forms. One was semi-liquids. And the third one was parenteral formulations. So I received training and schooling in these three disciplines.

"Question: Where did you go after that?

"Answer: I joined Pharmacyclics.

"Question: Is that in 1993?

"Answer: I left Hybritech in January of 1994, to be precise.

"Question: Okay.

"Answer: I joined Pharmacyclics in February of 1994.

"Question: What was your role at Pharmacyclics when you joined in 1994?

"Answer: I joined as a formulation scientist. I was to formulate our parenteral products and find contract manufacturers that can manufacture them for us so we can use them as clinical trial materials for our -- for our studies.

"Question: Let's go back. How long were you at Pharmacyclics? From 1994 to your until when?

"Answer: Until 2012.

"Question: What were your responsibilities for these lead development candidates?

"Answer: The main responsibility was to a -- come up with a suitable formulation so they perhaps could be evaluated in pre-clinical research and then develop that into a suitable formulation that could be used in the human clinical trials.

"If you find manufacturers that could manufacture the clinical trial materials for us, and all associated documentation, regulatory, specification generation, et cetera, that would make it into a clinical trial material.

"Question: And when you say you came up with suitable formulations, did you work with third-party companies to do so?

"Answer: We had in-house capabilities to prepare formulations and to conduct animal studies. So most of that work was done by myself with my hands, okay. At times we used the contract laboratories for analytical purposes for maybe methods that we didn't have in-house.

"Question: Were you the only one at Pharmacyclics that was responsible for formulating these drugs?

"Answer: Yes.

"Question: Can you give me some background as to your recollection of 2006 and what led to your involvement with the BTK inhibitor that ultimately became

ibrutinib?

"Answer. I was responsible for formulation development. The company decided that we are going to formulate all these BTK inhibitors, so I responded to that by starting developing the compounds, as I stated initially for a preclinical work.

"Question: What did you do when you started developing the compounds? You can answer.

"Answer: I personally prepared formulations that could be used in animal studies that the company decided to conduct.

"Question: How did you prepare these formulations?

"Answer: I was responsible for the formulation development. I also had responsibility of my formulation laboratory that allowed me to prepare formulations.

"Question: Did you -- were you responsible for selecting the excipients that were incorporated into the formulations, for example?

"Answer: I would choose the excipient -- the excipients that were appropriate for the preclinical studies, yes.

"Question: Were you responsible for choosing the excipients that were used in the human clinical trials ?

"Answer: Yes.

"Question: Were you working with others in developing the formulation for ibrutinib?

"Answer: I was responsible for the development, so I had some assistants from research assistance, some that may have worked for me for a time or two. But I drove the development.

"Question: Mr. Purro, I've handed you what's marked as Defendants' Exhibit 3. Let me know if you recognize this document?

"Answer: This is the e-mail that I wrote, so.

"Question: Can you tell me what this e-mail is about?

"Answer: This was written on or about the time when we were going to initiate the clinical trial manufacturing. I had worked with Pharmatek. They were my -- they were going to go to be my clinical trial manufacturers, right.

"So I'm giving them some guidance on a -- what appears to be a project plan. They used to split up the project plans into Phase 1, 2, 3, so forth. So it looks like I had reviewed the project plan and given some guidance on -- on -- comments on the different faces that they proposed.

"Question: At the time you wrote this e-mail, if you go to the fourth full -- fourth full paragraph down

where it says, 'we currently have two liquid formulations'.

"Do you see that?

"Answer: Yes.

"Question. At the time of this e-mail, did you have two liquid formulations, one being a solution and another a suspension for the PCI-32765 compound?

"Answer: I cannot make that out from this paragraph.

"Question. Well, you wrote that, we currently have two liquid formulations, one being a solution, the other a suspension; right?

"Answer: Yes.

"Question: What did you mean by that?

"Answer: Yes, so we must have had two liquid formulations that we were using in pre-clinicals, right.

"Question: And in the following paragraph, you were asking Pharmatek to develop a capsule formulation that is intended to replace the -- the liquid formulations that you had already; right?

"Answer: I can read what it says here. Okay? And the -- we would have provided Pharmatek with a proposed formulation and asked them to develop that into a capsule formulation that can be used in clinical trials based on our leadership.

"Question: Okay. And this e-mail indicates you

were asking them to develop a capsule formulation to replace the formulations that you had come up with, correct?

"You can answer.

"Answer: We would be asking to develop a material in the form of a capsule that we can take to clinical trials. So there's more steps than just a -- this has to go into the GMP system. So it has to be developed so you can manufacture it. That's what we're asking them to do here.

"Question: Is it fair to say, then, that Pharmatek is a company outside Pharmacyclics that you worked with to develop the formulation for PCI-327652?

"Answer: Pharmatek is a company that we worked with to prepare the capsules that we can use in human clinical trials, and in that process, there needs to be some adjustment so you can manufacture the capsule in a -- in a reasonable manner. And that's a collaborated effort. The formulation was given by us.

"Question: What formulation did you provide Pharmatek?

"Answer: We provided the formulation that had the excipients and the approximate ratios spelled out.

"Question: Have you seen any documents that show the formulation, including the excipients and the approximate ratios, that you specifically provided to

Pharmacyclics?

"Answer: I have seen a project plan, or we asked them to evaluate the manufacturability with an allowance to just one of the components, which is a -- which was used as a diluent.

"Question: So you've seen a project plan asking them to evaluate the manufacturability of ibrutinib with one of the components that was used as a diluent?

"Answer: Yes.

"Question: What about any other components, any other components that were identified to Pharmatek by you or anyone else at Pharmacyclics?

"Answer: A project plan spelled it out particularly, that the diluent may have to be adjusted in order to -- to get a capsule that's full, which is a pretty -- pretty common thing to do.

"Question: Mr. Purro, you can proceed to answer my question, which was, was Pharmatek responsible for adjusting the diluent?

"Answer: We had asked them to evaluate the diluent. We were responsible for accepting the parameters that they came up with. They were the manufacturers and are best suited to evaluate that, bring it back to us and for us to say, yes, that's good, or, no, that's not good.

"Question: Were the excipients used in the

liquid formulations that you developed for the animal studies the same excipients used in the capsule formulation Pharmatek developed?

"Answer: I would have to think no. There might have been overlap, but usually the excipients are quite different for liquid than -- than the solid formulations.

"Question: If I understood your previous testimony, it was Pharmatek that was responsible for adjusting the excipients and then you would sign off on it; is that right?

"Answer: Pharmacyclics would sign off on the batch records. So that's the ultimate control that you have over the formulation in the manufacturing process. Without that, manufacturing would not commence.

"Question: Right. But as far as what decisions are made on the manufacturing side with respect to what excipients were to be used, the amounts, those types of things, Pharmatek was making those decisions. Correct?

"Answer: No.

"Question: Was it solely you that was making those decisions, Purro?

"Answer: It was me representing Pharmacyclics that made these decisions.

"Question: When you say these decisions, what

do you mean?

"Answer: Of what is going to be in the formulation.

"Question: Pharmatek had no involvement whatsoever in deciding what went into the formulation of the capsules; is that your testimony?

MS. ANDERSEN: Asked and answered.

THE WITNESS: We would consider their opinion. If there was an issue where, hypothetically speaking, which I guess I shouldn't do, if there was an issue with an excipient that they couldn't use in the manufacturing facility, we would obviously consider that. But other than that, no.

"Question: You would consider their opinion. So what were you asking Pharmatek to do?

"Answer: We asked them to take our formulation and make it so it can be prepared on the GMP for clinical trial use.

"Question: Is it your testimony today that they did not change any of the formulation that you provided to them?

"Answer: We had talked about the diluent, okay? So that's -- that's one thing that they did to adapt the process and agreed to that.

"(Exhibit 4 was marked for identification and

attached hereto.)

"Question: Mr. Purro, I've handed you what's been marked as defendants' Exhibit 4. Do you recognize this document?

"Answer: Yes.

"Question. What is this document?

"Answer: It's an IND Section, 3.2.P.2 pharmaceutical development.

"Question: What does this document show?

"Answer: This document shows the pharmaceutical development as it was at the time of the filing of the IND.

"Question: Okay. If you go to page 2 of the document, there's a summary presented there under the heading 3.2.P.2 pharmaceutical development.

"Do you see that?

"Answer: Uh-huh.

"Question: Were you involved in preparing this submission to the FDA?

"Answer: Yes.

"Question: Okay. Were you involved in drafting the summary presented on page 2?

"Answer: Yes.

"Question: Okay. And then an additional dosage strength, the next sentence, of 140 milligrams PCI-32765 was developed and manufactured by Pharmatek beginning in

March 2010.

"Do you see that?

"Answer: I see that.

"Question: Pharmatek developed the 140-milligram PCI-32765 dosage strength?

"Answer: It is -- later in the paragraph, it's explained what they did, meaning that they adjusted the amount of microcrystalline cellulose, and we directed them to do so.

"Question: We'll get to the excipients in a second. I'm asking about the dosage strength.

This document states that Pharmatek developed the additional dosage strength at 140 milligrams, does it not?

"Answer: We asked them to do that. It was under our guidance and under our direction. I asked them to come up with a 140 dosage form that fit in between the 40 and the 200.

"Question: You asked them specifically to create an additional dosage strength of 140?

"Answer: Yes.

"Question: In the last paragraph it states, the formulation process was transferred from Pharmatek to Aptuit where it was modified to allow for mechanized capsule filling.

"Do you see that?

"Answer: I see that.

"Question: Why was the formulation process transferred from Pharmatek to Aptuit?

"Answer: It was transferred to allow for mechanized capsule filling.

"Question: Why -- why did you want to allow for mechanized capsule filling?

"Answer: So the batch sizes could get scaled up.

"Question: And it states here that magnesium stearate and API-glidant was added to the formulation to improve the mechanized process.

"Do you see that?

"Answer: Uh-huh.

"Question: Did you come up with a concept of using a diluent to allow you to reduce the dosage of a dosage a form to a level that you would like in a set unit?

"Answer: In the case of ibrutinib, I came up with the idea of using a diluent to bring the formulation from a 200-milligram dose dosage strength down to a 40-milligram dosage strength.

"Question: Okay. Were you the first one to come up with the concept of using croscarmellose sodium to

increase the disintegration rate of a capsule?

"Answer: In the case of ibrutinib, I added the croscarmellose sodium to increase the disintegration rate of the ibrutinib capsule.

"Question: Yeah. Sodium lauryl sulfate is a surfactant that increases PCI-32765 solubility in aqueous media, right?

"Answer: I see that this is stated here, that sodium lauryl sulfate is a surfactant that increases solubility in aqueous media.

"Question: And who -- who came up with the idea to use a glidant?

"Answer: We did.

"Question: Turn to page six of the pharmaceutical development report. In the section entitled 32P-23, manufacturing process development. If you go to the third -- sorry -- fourth paragraph down at the bottom of the page, it states that, a third intermediate dosage strengths, 140 milligrams was developed by Pharmatek. Do you see that?

"Answer: Yes.

"Question: And did you write this section, Mr. Purro?

"Answer: Yes.

"Question: What did you mean by, a third intermediate dosage strength, 140 milligrams was developed

by Pharmatek?

"Answer: We needed an intermediate dosage strength. And we asked Pharmatek to figure out how we can make 150-milligram dosage strength. I already mentioned that we instructed them that they can use more diluent as needed to arrive at that 140-milligram dosage strength. And it says in here again, accept that the inner diluent is used, just a final capsule.

"Question: This states that Pharmatek developed the dosage strength, does it not?

"Answer: It says nothing about having developed the formulation.

"Question: Sure. This is talking about the fact that Pharmatek developed a dosage strength for PCI-32765 at 140 milligrams; right?

"Answer: Pharmatek developed the manufacturing process via dilution.

"Question. Well, look, Mr. Purro, there are specific words used on this document. The sentence reads, a third intermediate dosage strength, 140 milligrams was developed by Pharmatek.

"Answer: Okay.

"Question: Okay? Do you agree with me there that's what it says?

"Answer: Yes, that's what it says.

"Question: Okay. And do you have any reason to doubt the accuracy of that statement that was submitted to the FDA?

"Answer: I'm a scientist and I wrote it as a scientist. And for me, that was a -- that is an accurate statement. And what is meant by develop is up to the interpretation.

"Question: Up to the FDA's interpretation or up to anyone's interpretation?

"Answer. Well, the word develop can be interpreted by anyone.

"Question: Would it have been Pharmacyclics' practice to include a statement that was ambiguous or false to the FDA in an IND submission?

"Answer: Excuse me?

"Question: Would it have been Pharmacyclics' practice to include a statement that was ambiguous or false --

"Answer: No.

"Question -- to the FDA in an IND submission?

"Answer: No.

"Question: No?

"Answer: No.

"Question: So the statement included in here, to the best of your knowledge, is accurate and true?

"Answer: The statement is true.

"(Exhibit 6 was marked for identification and attached hereto.)

"(Exhibit 7 was marked for identification and attached hereto.)

"(Exhibit 8 was marked for identification and attached hereto.)

"(Exhibit 9 was marked for identification and attached hereto.)

"(Exhibit 10 was marked for identification and attached hereto.)

"(Exhibit 11 was marked for identification and attached hereto.)

"(Exhibit 12 was marked for identification and attached hereto.)

"Question: Mr. Purro, the court reporter is handing you documents that have been marked 6 through 12. I will represent to you that these are the patents that you have been identified or designated by plaintiffs to testify about.

Are you familiar with these documents, Mr. Purro?

"Answer: I'm somewhat familiar with them.

"Question: Okay. Let's start with Exhibit 9. Do you have that in front of you? If you turn to the second

page, Mr. Purro, what is this document?

"Answer: It's a United States patent.

"Question: And it's a United States patent 9,725,455.

"Answer: Correct.

"If I refer you to this patent as the '455 patent, will you understand what I'm talking about?

"Answer: Yes, I will.

"Question: All right. And on the left-hand column, there is a listing of inventors.

"Do you see that?

"Answer: I see that.

"Question: And it lists yourself first. It also lists a man named Mark Stephen Smyth. It lists Erick Goldman and it lists David G. Wirth:

"Do you see that?

"Answer: I see that.

"Question: Is it your understanding that all four of these individuals are named inventors -- strike that.

"Is it your understanding that all four of these individuals are inventors of the inventions claim in the '455 patent?

"Answer: That is my understanding.

"Question: Do you have any knowledge

independent of the fact that they are listed in -- on the face of the patent as to whether they are inventors of the inventions claimed in the '455 patent?

"Answer: I have worked with two of the listed inventors during my time at Pharmacyclics. I know that they were involved in the ibrutinib project.

"(Reporter clarification.)

"Answer. They were involved in the ibrutinib project, so I have no reason to doubt that they're not inventors.

"Question. What is your understanding of the invention of the '455 patent?

"Answer: There was -- there's lots of work described in here.

"Question: I'm asking you what your understanding is. If you have one, please tell it to me. If you don't, tell me, that, too.

"This patent contains part of the work that I did for Pharmacyclics. That's how I understand it. It is not spelled out in the title of it, but it's in the body of the document.

"Question: Let's turn to column 78 of this patent.

"If you go down to the bottom of the column, you see there's a line 50. It states: What is claimed is.

"Do you see that?

"Answer: I see that.

"Question: And you see under that is claim 1. Do you see that?

"Answer: Yes, I do.

"Question: Claim 1 reads, a crystalline form A of -- I'm just going to say ibrutinib -- that has an X-ray powder diffraction (XRPD) pattern can comprising 2-Theta peaks at 5.7 plus or minus .1 degree, 18.9 plus or minus .1 degrees and 21.3 plus or minus .1 degrees.

"Do you see that?

"Answer: Uh-huh.

"Question: What is your contribution to claim 1?

"Answer: I do not write this patent.

"Question: That is not what I asked. What is your contribution to claim 1?

"Answer: What is my contribution? Is that what you're asking?

"Question: Yes.

"Answer: To claim 1? I did not contribute to claim 1.

"Question: Okay. Let's go to claim 2. Can you read that to yourself and let me know what your contribution to claim 2 is?

"Answer: I did not contribute to the crystalline forms.

"Question: You didn't contribute anything to the crystalline forms of ibrutinib?

"Answer: I did not contribute to the crystalline forms. Okay.

"Question: What did you contribute to claim 1 through 30 of the '548 patent?

"Answer: Again, the patent that I contributed to is listed under the Related Application Data, and I would have to further review this.

"Claim 27 does mention a pharmaceutical formulation that's using the crystalline form of claim 1, which is ibrutinib and at least one pharmaceutically acceptable ingredient. I don't know exactly how to interpret that. I don't write -- I didn't write this patent. Okay.

"Question: You had nothing to do with identifying crystalline forms of ibrutinib during your work on the ibrutinib project; is that correct?

"Answer: I answered that. I said, no, I did not.

"Question: All right. So claim 27. Any other claims that you believe you contributed to in the '548?

"Answer: I can't answer with certainty, so I don't know.

"Question: Can you turn to Exhibit 10. What is this document, Mr. Purro?

"Answer: It's a U.S. Patent 9,713,617.

"Question: I'll refer to this as the '617 patent; is that okay?

"Answer: Uh-huh.

"Question: Again, the inventors listed here are yourself, Mark Smyth, Erick Goldman Dave Wirth; correct?

"Answer: Correct.

"Question: Was it your idea to come up with an oral administration -- or oral formulation for ibrutinib?

"Answer: That at some point was a company decision to develop an oral -- an oral formulation, and I came up with the oral formulation for ibrutinib. That was a directive that I received to accomplish a company goal.

"Question: Did you do that by yourself?

"Answer: Yes, I did.

"Question: Did you -- so nobody else contributed to the oral formulation of ibrutinib that is claimed in claim 1 ?

"Answer: I was responsible for the development, for formulation development, at Pharmacyclics. I was the

head of formulation development, and I developed this formulation either directly or by directing another employee to perform experimentation on behalf of the projects.

"Question: So what do you mean without being excessive? So too much lubricant would be -- wouldn't work?

"Answer: There are ranges where a lubricant would -- would -- would be excessive and you wouldn't want -- wouldn't want to use it at that level. It's --

"Question: What ranges would those be?

"Answer: That depends on the formulation. Greatly depends on --

"Question: If you can pull up Exhibit 6, please.

"Do you recognize this document, Mr. Purro?

"Answer: The document is a United States patent 10294231.

"Question: So the '231 patent, if I refer to that, refer to it that way, is that okay?

"Answer: Yes.

"Question: You have not made an ibrutinib tablet formulation; correct?

"Answer: I have --

"Question: I'm sorry?

"Answer: I have not.

"Question. Now, how did you go about making the ibrutinib capsule formulation?

"Answer: I considered all the factors.

"Question: So there are at least two instances where you've had a capsule and tablet formulation contain the same API that you have formulated that have made it to human clinical trials, right?

"Answer: Right.

"Question: And in those two -- and in at least those two instances, the capsule formulation that you formulated, what -- strike that.

In at least those two instances, you formulated the capsule formulation prior to formulating the tablet formulation that contained the same API; correct?

"Answer: Yes.

"Question: Now, earlier you had mentioned that you -- when you had worked on the ibrutinib capsule formulation, you at least based your -- at least part of your research and work on the solutions and suspensions.

"So my question for you is, in formulating these, at least these two instances with the tablet formulations, did you at least base your research in part on the capsule formulation?

"You can go ahead and answer.

"Answer: I would take the capsule formulation

into consideration.

"Question: Why would you take the capsule formulation into consideration?

"Answer: Because it provides scientific data.

"Question: What scientific data does it provide?

"Answer: Most importantly, the dissolution profile.

"Question: Anything else?

"Answer: The dissolution profile.

"Question: And besides the dissolution profile, is there anything else that you would consider from the capsule formulation in formulating the tablet formulation?

"Answer: It would, at the minimum, provide compatibility data with the excipients used in the capsule formulations.

"Question: Anything else?

"Answer: No.

"Question: You mentioned that it would be under the assumption that you would want to match the dissolution profiles.

"Would you ever want to match a dissolution profile when making a tablet formulation that's already been formulated as a capsule formulation?

"That's already been formulated as a capsule formulation containing the same API?

"Answer: Yeah, you might want to do that.

"Question: Why would you want to do that?

"Answer: You would want to do that if you want to change the format from a capsule to a tablet without it impacting the in vivo performance.

"Question: So when formulating a tablet formulation where there was a prior capsule formulation that contained the same API, you would consider the compatibility of the excipients in the capsule formulation with the API in formulating the tablet formulation that contained the same API; is that correct?

"Answer: Not correct.

"Question: Why is that not correct?

"Answer: You start from scratch. I was saying that it's nice to know if a certain excipient is compatible. Doesn't mean you want to use it. It's just nice to know. You asked me what other information would you consider. I said dissolution and then I also said -- since I have compatibility data, that would be something that I would know.

"Question: So you would not consider any of the excipients or the way they interact with the API in formulating the tablet formulation that was previously

formulated as a capsule formulation with the same API.

"Is that your testimony?

"Answer: Starting from scratch to me means I have all excipients available, even the ones that I previously used in a capsule formulation. I will not give them priority, okay?

"Question: Now, if you wanted to match a -- the -- a tablet formulation of the capsule formulation that was previously formulated with the same API, you would consider the -- the excipients that were compatible with the API in the capsule formulation, correct?

"Answer: Again, I would consider all excipients.

"Question: And are you aware of the specific reference -- you mentioned that those are in the literature. Are you aware of those particular references, or are you just speaking generally?

"Answer: Speaking generally that you're aware that there's an excipient book out there and that's obviously a key reference that every formulator will go to.

"Question: Now, that key reference you're referring to is the Handbook of Pharmaceutical Excipients. Is that correct?

"Answer: Yes.

"Question: And that would have been used commonly for both capsule and tablet formulation, right?

"Answer: Yes.

"Question: You formulated the Imbruvica, ibrutinib capsule formulation, correct?

"Answer: Yes.

"Question: I'm going to refer you to Exhibit 10. Exhibit 10 is the '617 patent, correct?

"Answer: Exhibit 10.

"Question: Exhibit 10?

"Answer: Exhibit 10, you can refer to as the '617 patent.

"Question: I will direct you to column 78. Looking at claim 1. Looking at that combination, how many different formulations would come within that claim?

"Answer: I'm sorry, how many formulations followed in that claim?

"Question: How many combinations would fall within that claim?

"Answer: Do you mean theoretically how many could fall into that claim?

"Question: Yes.

"Answer: Having four variables, you'll end up with an infinite number of combinations.

"Question: Would you expect all those diluents, disintegrants, surfactants, lubricants in combination to work in an ibrutinib formulation?

"Answer: No, I would not expect any combination of any of the listed class of excipients to act in the same way.

"Question: And why would you not expect any combination of any listed class of excipients to act in the same way?

"Answer: All these excipients, even though they are in different classifications, they have different properties and they will behave different, especially in combination with each other. If they didn't, we wouldn't be able to formulate anything. Everything would be the same all the time.

"Question: Would you need to test the different combinations?

"Answer: Of course.

"Question: So my follow-up question is, when you say of course you need to test the different combinations, what kinds of tests would you need to perform?

"Answer: Dissolution, disintegration, stability.

"Question: Any other tests?

"Answer: That would be the focus, right. There

might be other tests, but that would be the most important test that I would conduct.

"Question: What would be some not as important tests?

"Answer: Water content.

"Question: And when you say water content, what does that mean?

"Answer: That means you measure how much water is in -- in a capsule, and if that changes over time.

"Question: Any other tests?

"Answer: There's many others. I gave you some examples of the ones that are more relevant to the -- to the testing.

"Question: When you say relevant to the testing, do you mean relevant to the ibrutinib formulation?

"Answer: No. Relevant to how you would evaluate the pharmaceutical formulation in general, which also would include the ibrutinib formulation. But these were general terms of what I would test for.

"Question: I'd direct your attention to Exhibit 12. And what is Exhibit 12?

"Answer: It's a United States Patent 10,294,232.

"Question: Okay if I refer to it as the '232 patent?

"Answer: Yes.

"Question: I'm going to direct you to column 78.

"Looking at claim 1 at the bottom of column 78 --

"Answer: Uh-huh.

"Question: -- how many different formulation combinations would fall within claim 1?

"Answer: I mean I can't really put a limit on it, okay? It could be -- it could be hundreds of different combinations under these conditions. Just by the fact that it's one or more disintegrating agent right there, that gives me hundreds of combinations.

"Question: Sure. How would you go -- how would you go about determining whether each specific combination of diluent, disintegrant, surfactant, lubricant works in the ibrutinib formulation listed here in claim 1?

"Answer: Okay. Besides testing each and every combination that you propose, there is a methodology that's called designing experiments, where you could design an experiment that would give you a little broader range when you don't have to test each individual one. That's kind of a complicated approach, but regardless, to answer your questions, you would have to experimentally test a lot of formulations within that range.

"Question: Okay. I'd like to mark this as Exhibit 19.

"(Exhibit 19 was marked for identification and attached hereto.)

"Question: It's a document entitled 3.2.P.2.2, drug product formulation development. And it is Bates numbered IMBPCY00150028 to IMBPCY00150338.

"Have you seen Exhibit 19 before, Mr. Purro?

"Answer: Yes, I have.

"Question: And what is it?

"Answer: This is the formulation development section of the NDA.

"Question: Does this exhibit describe, in part, a number of ibrutinib formulations that you developed?

"Answer: Yes, it does.

"Question: You developed a number of capsule formulations for ibrutinib, correct?

"Answer: Yes.

"Question: And you developed a number of solution and suspension formulations for ibrutinib, correct?

"Answer: Yes.

"Question: I'd like to turn to Table 3 in Exhibit 19.

"Answer: Uh-huh.

"Question: What information is contained in

this table?

"Answer: These are formulation component and compositions that were used in Phase 1 and 2 clinical trials by Pharmacyclics. They were prepared by Pharmatek. They prepared the clinical trial materials for us.

"Question: And these are formulations, capsule formulations, that you developed?

"Answer: That is correct.

"Question: And in the formulations listed in Table 3, you tried different amounts of microcrystalline cellulose. Do you see that?

"Answer: Yes.

"Question: You tried different amounts of croscarmellose sodium? Is that right?

"Answer: They are different amounts, but the percentage is -- is the same.

"Question: And you tried different amounts and percentages of sodium lauryl sulfate; is that right?

"Answer: Yes.

"Question: And you tried different percentages of the active ingredient; is that right?

"Answer: That's correct.

"Question: Sure. Did you know without testing the amounts of magnesium stearate with the combination of the other excipients whether or not it was -- would be

successful as an excipient in the formulation that you ultimately chose?

"Answer: We did not know that. We had to try it out. We did have formulations here that contain a higher amount of magnesium stearate. So it was a fairly safe assumption that a lower amount would not affect the performance of the formulation.

"Question: So you had to conduct experiments in order to know which range of magnesium stearate would be appropriate in the ultimate formulation?

"Answer: Yes."

(End of videotaped deposition.)

THE COURT: All right.

MS. CLAYTON: Your Honor, I believe Alvogen intends to call its witness.

THE COURT: Okay. Great.

MR. HANNA: Dr. Fassihi, can you hear us?

MR. SIPES: I'm sorry, Your Honor. We're ready to proceed.

THE COURT: Sorry. I was on mute. I didn't realize it. Yes, you should go ahead. Sorry.

...DR. REZA FASSIHI, having been duly sworn/affirmed as a witness, was examined and testified as follows ...

BY MR. HANNA:

Q. **Welcome back, Dr. Fassihi.**

A. **Thank you.**

Q. **I understand you created a set of demonstrative exhibits?**

A. **Yes, I did.**

Q. **How did you create those demonstrative exhibits? Can you hear us, Dr. Fassihi?**

A. **Yes, yes.**

Q. **Okay. How did you create those demonstrative exhibits?**

A. **I created them after consulting with Alvogen's counsel.**

Q. **Now, a few days ago, you discussed Alvogen's tablets. Are there any drawbacks to formulating API in a capsule dosage form?**

A. **Yes. There are a number of drawbacks.**

Q. **And what are they?**

A. **I have listed them in my slides. So capsules basically have a limited volume to contani the active ingredient and excipients. It can pick up moisture and release moisture into the formulation, which makes it unstable. Capsules are too large to be swallowed by patients and it interferes with compliance.**

Q. **What happens if the required amount of API exceeds the fixed volume of the capsule?**

A. **Well, in that case, they just have to increase the number of capsules the patient has to take.**

Q. **Now, how would formulating the API into a tablet dosage form address that problem?**

A. **Well, tablets are basically a very advanced consolidated powder. Therefore, you can put much larger amount of API together with excipients. It makes advanced tablets that account for a much larger goal.**

Q. **If the amount of API in a capsule were a concern for a pharmaceutical company, why not manufacture a bigger capsule?**

A. **Well, the capsule sizes are such that typically, I think you have all taken Amoxicillin capsules, for example, and that is the size number one or size number zero. That is our limit. If it is anything larger than that, patient cannot swallow. So that is the limitation.**

Q. **Now, if the amount of API in a capsule were concerning to a pharmaceutical company, why not ask the patient to take more capsules?**

A. **I think what has happened, when it's large, often patients have to take four or five capsules per day and that is very inconvenient.**

Q. **What is the most common route of administration for pharmaceutical formulations?**

A. **It's oral route of administration.**

Q. **And what is the BCS system?**

A. **The BCS is, BCS stands for Biopharmaceutics Classification system. It is a system developed by FDA to basically define in terms of solubility and permeability.**

Q. **How is ibrutinib characterized according to the BCS in terms of its solubilities and permeability?**

A. **It has been designated BCS Class II, which is low solubility, high permeability.**

Q. **What types of excipient are used in tablet formulations?**

A. **I have a demonstrative that I have that appears on the slide. Generally, what you need to make a tablet, you need fillers, disintegrant, binders, glidants, lubricants and surfactants.**

Q. **Now, why are fillers or diluents used in tablet formulation?**

A. **Well, the tablets, they, they should be compressed and therefore come to a stability consolidation is something that depends on the characteristics of the fillers. That's what they use here.**

Q. **And what is the most common filler used in tablets?**

A. **Currently, I think lactose and also microcrystalline cellulose. Those are the main, main ones.**

Q. **Why are disintegrants used in tablet formulation?**

A. **Well, tablets are compressed in the tableting machine**

as maybe thousands of kilogram host, so they are very strong and damp and they need to be -- break apart once they come in contact with water. So we need disintegrant to break it up.

Q. **And what is an example of a commonly used disintegrant?**

A. **The most common one is, for example, croscarmellose sodium.**

Q. **Why are binders used in tablet formulations?**

A. **Once again, because tablets, they need the thread and binders contribute to that function, that property of the tablet to provide strands and therefore we need to use binders.**

Q. **What is an example of a commonly used binder?**

A. **Again, most commonly used is polyvinylpyrrolidone.**

Q. **Why are glidants used in tablet formulation?**

A. **The tableting process is very fast. In tablet making pharmaceutical companies, they provide 5 -- 6,000 tablets per minute. That means the powder, which is blended together as a formulation, has to flow into the machine. For that reason, glidants are used and they help flow a powder into the machine.**

Q. **What is the most commonly used glidant?**

A. **It is colloidal silicon dioxide, which is extensively used.**

Q. **Why are lubricants used in tablet formulations?**

A. **Lubricants are used again because the compression requires a lot of work. So the consolidated tablet, it stays in the machine and has to be ejected.**

So lubricants are added to help ejection of tablets from the machine so that the --

Q. **Are lubricants commonly included in tablet formulation?**

A. **Yes.**

Q. **Now, what is the most commonly used lubricant?**

A. **Magnesium stearate is the one that is extensively used.**

Q. **Why are surfactants used in tablet formulations?**

A. **Often the formulation that, for example, use magnesium stearate, if there's low solubility, magnesium stearate is very hydrophobic. So manufacturing formulators, they add a hydrophilic surfactant to basically create a balance in there.**

Q. **What is a commonly used surfactant?**

A. **The most commonly used is sodium lauryl sulfate.**

Q. **Is it common for a formulator to formulate a tablet with the same inactive excipient used in a prior capsule formulation containing the same API?**

A. **Of course. If there already is a product which is approved by FDA and on the market such as, for example, in**

this case, as a capsule, that will be our starting point, that we use the capsule. Water is used there. We try a few times to see if it can be comparable. If it cannot be comparable, then we look for other resources such as excipients and published information to basically to experiment, routine experimentation to come up with a tablet formulation.

Q. **And why is it common to include the same excipients in tablet formulation previously used in a capsule formulation?**

A. **Well, it is from a regulatory point of view, a laborious process, and if something is already there, the approach is to use those that are FDA approved. The FDA is very confident with that and you need to play around with an another two or three to build your tablets.**

Q. **Are there any commercially available ibrutinib products in the U.S.?**

A. **Yes.**

Q. **What are they?**

A. **There are two products on the market, Imbruvica capsule and Imbruvica tablets.**

Q. **And when did FDA approve Imbruvica capsules?**

A. **As I have shown on my slide, the capsule was approved in 2013.**

Q. **Is DTX-1413 the Imbruvica 2013 label?**

A. **Yes, that's correct.**

Q. **And when did it publish?**

A. **That was published in November 2013.**

Q. **What indications did FDA approve Imbruvica capsules for in 2013?**

A. **The indication for Imbruvica is for treatment of mantle cell lymphoma.**

Q. **And what is the recommended dose for treating MCL according to the level?**

A. **The label indicates 560 milligrams to be taken orally once a day.**

Q. **Are you aware of any changes to the recommended dose for the indication for Imbruvica capsules?**

A. **No changes.**

Q. **In 2013, how much ibrutinib was formulated into each Imbruvica capsule?**

A. **Again, as the label shows, each capsule contains 140 milligrams, so in order to come up with a dose of 560, which is essential for treatment, as they have said, patient has to take four capsules and, of course, compliance with that number of doses that one has to take is just literally too much.**

Q. **Do Imbruvica capsules contain any inactive excipients?**

A. **Yes, it does.**

Q. **And what are they?**

A. **I have looked at the label again and they describe croscarmellose sodium, magnesium stearate, microcrystalline cellulose and sodium lauryl sulfate. Yes.**

Q. **Did FDA approve those excipients in combination with ibrutinib as of 2013?**

A. **Yes.**

Q. **And, Dr. Fassihi, can you please provide a summary of your opinions in this case?**

A. **My opinion, I have looked at the '857 patent and I've read the claim 30 and 37 of '857. And based on what I have looked at and I've read the literature, the claims are invalid and obvious and also for lack of written description.**

Q. **And is there a particular date that you applied for priority in terms of the prior art?**

A. **Yes. The priority date for '857 was March 10th, March 3, 2015.**

Q. **Please turn to JTX-0049.**

Dr. Fassihi, what is JTX-0049?

A. **This is the represented patent, '857.**

Q. **And if you continue on. Did you review the prosecution history in connection with the '857 patent?**

A. **Yes, I did.**

Q. **And why did you review the prosecution history?**

A. **Just I wanted to understand the, you know, the claims**

and I went back there. I looked at prosecution history.

Q. **And is JTX-0049 the prosecution history that you reviewed?**

A. **Yes, it is.**

Q. **Dr. Fassihi, were FDA approved solid oral dosage formulations of ibrutinib publicly available prior to March 3rd, 2015?**

A. **I'm sorry. Can you repeat the question?**

Q. **Yes. Were FDA approved solid oral dosage formulations of ibrutinib publicly available prior to March 3rd, 2015?**

A. **Of course. The Imbruvica capsule was on the market as of 2013, yes.**

Q. **Does the Imbruvica 2013 label identify the amount of ibrutinib in Imbruvica capsules?**

A. **Yes, it does.**

Q. **And does it identify -- is that the 140 mgs that we looked at previously?**

A. **That's correct.**

Q. **Does the Imbruvica 2013 label identify the amount of ingredients in the Imbruvica capsule?**

A. **Not amount of ingredient, no.**

Q. **Was there any prior art that described an Imbruvica capsule formulation having the same API and excipients as an Imbruvica capsule?**

A. **Yes. There was a publication '172 patent, which also**

was from Pharmacyclics, which was published in 2013.

Q. And is that DTX-1399?

A. That's correct.

Q. Where in the '172 publication does it describe an Imbruvica capsule formulation having the same API and excipient as an Imbruvica capsule?

A. So if you -- here in the Table 5, and I'm looking at third column in there, which shows 140 milligrams, and it lists everything which is in the capsule. It does say capsule formulation on the top of the table.

Q. And --

A. So column 3 describes the crystalline compound 1, which is ibrutinib. It describes microcrystalline cellulose, croscarmellose, sodium lauryl sulfate and magnesium stearate.

Q. Did the '172 publication only disclose ibrutinib capsule formulations?

A. No. It also disclosed a tablet formulation.

Q. And where in the '172 publication did it disclose a tablet formulation?

A. As I have shown on the slide, it is Example 11, Table 6, and it -- right below this example, immediate release tablet. The list of ingredients are there as well as the range, percentage range of each.

So, for example, if you have crystalline

compound 1, which is a five percent ibrutinib, you have hypromellose, lactose, magnesium stearate, and a percentage range.

Q. **Now, what is hypromellose?**

A. **Hypromellose is a binder that was added.**

Q. **Dr. Fassihi, besides the '172 publication, were there any other publications that described ibrutinib tablet formulations prior to March 3rd, 2015?**

A. **Yes. In the publication of Goldstein in 2014, which is a different slide. That was published, also describes a tablet formulation of ibrutinib.**

Q. **And when you refer to the Goldstein reference, you're referring to WO 2014/004707?**

A. **That's correct.**

Q. **And that's DTX-985?**

A. **Yes.**

Q. **How many tablet formulations are disclosed in Goldstein 2014?**

A. **I believe there are three examples there that relate to solid dosage form.**

Q. **With respect to tablets?**

A. **Yes.**

Q. **Now, what ingredients are included? Does Goldstein 2014 describe any immediate release tablet formulation of ibrutinib?**

A. **Yes. Both Example 2 and Example 3. Let's look at Example 2. It says right on the top, ibrutinib and/or pharmaceutically acceptable salt in non-enteric delayed time released tablet press. So it measures that.**

And in the first paragraph starting at to make immediate release tablets of ibrutinib, and then they describe all the limits and how to proceed. And they eventually make, get to the point for the end of the paragraph, the powders are blended. Powder blend is then tableted using conventional tablet. That is how the tablets are made.

Q. **Now, what ingredients are included in the immediate release tablets disclosed in Goldstein 2014?**

A. **Well, it describes, these are in yellow highlight ibrutinib. Then there is microcrystalline, lactose, those two together. There's a starch. Further, the sodium starch glycolate, magnesium stearate and silicon dioxide.**

Q. **Now, what is starch?**

A. **Starch is the diluent and the binder that is used.**

Q. **And what is sodium starch glycolate?**

A. **That is a disintegrant.**

Q. **Does Goldstein 2014 disclose the amounts of the ingredients in its immediate release tablets?**

A. **Yes. In Example 2, which is on the right-hand side of this description, this is a description of the, all of those**

ingredients in kilogram amount.

Q. **Now, would a POSA have understood how to convert the kilogram amount to weight-by-weight percentage?**

A. **Sure. Yes. That's what I've done on the third column. That is my calculation that I've provided. So those are exact percentages of those kilogram quantities.**

Q. **And so what were the weight percentages of each ingredient in Goldstein's 2014 immediate release tablet?**

A. **Ibrutinib was 80.9 percent. Microcrystalline cellulose with lactose together, 8.1 percent. The starch, 7.3 percent. Sodium starch glycolate, 3.2. Magnesium stearate, 0.3 percent. Silicon dioxide. 0.2 percent.**

Q. **And you said 80.9 percent. Is that with respect to ibrutinib?**

A. **Yes.**

THE COURT: Stop for one second. Go ahead.

Q. **Is Goldstein's 2014 immediate release tablet a high load solid tablet formulation of ibrutinib?**

A. **Yes, it is.**

Q. **And why is it a high load solid tablet formulation?**

A. **Well, you know, the tablets that contain 50 to 90 percent of the API are considered a high load formulation.**

Q. **And --**

A. **Tablet. Yes.**

Q. **And why do you believe that the solid tablet formulations, immediate release tablet formulation is a high load tablet formulation?**

A. **Well, this one has 80.9 percent, so that is very high. I said between 50 and 90 percent is considered a high load formulation.**

Q. **You mentioned that Goldstein 2014 disclosed other tablet formulations. Can you please describe those?**

A. **Yes. Example 3 is another one, and it also describes more or less the same components, I believe. It is an immediate release tablet using the same ingredients and it has different, different amounts.**

Q. **What was the weight percentage of ibrutinib in the coated tablet disclosed in Example 3 of Goldstein?**

A. **So these are the kilogram quantities of Example 3 and I did the calculation and the ibrutinib contents of this formulation was 60.98 percent.**

Q. **And how did you determine that?**

A. **Well, the kilogram quantity is there and the total of immediate release, the total is 12.38 because the remainder is the coating. So we are looking at the tablet, the tablet itself before coating dissolved. So it's 4.36 kilograms, and we have each of them in kilograms which we can easily calculate. And based on that, 60.98 is the amount of ibrutinib in that.**

Q. **Does Goldstein 2014 require that the tablet formulations described in Example 2 and three include a delayed release or modified release coating?**

A. **That is not a requirement, no.**

Q. **How do you know that?**

A. **Well, because it describes, you know, in Example 3, it says it is an immediate release right at the beginning. As in Example 2 to make immediate release tablets, and it goes on to describe it. And you make your immediate release tablets. And then, further, if you want to coat it, then you may or may not.**

Q. **Does Goldstein 2014 identify the immediate release tablet that you identified earlier as an intermediate?**

A. **No.**

Q. **Before March 3rd, 2015, how would a POSA know whether a particular excipient was considered to be safe and effective in humans?**

A. **Well, the Handbook of Pharmaceutical Excipients is a compendium that every, you know, POSA would look at the FDA's added list. Excipients that are regarded as safe.**

Q. **And is DTX-1625 the Handbook of Pharmaceutical Excipients.**

A. **That's correct.**

Q. **And what is generally in the Handbook of Pharmaceutical Excipients?**

A. **In the Handbook of Pharmaceutical Excipients, each of the excipients has a description in terms of physical properties, moisture content, so they give a full description of each of the excipients in there so that we can look and identify what we wanted.**

Q. **And when did the Handbook of Pharmaceutical Excipients publish, the version that you relied on?**

A. **This is the third edition, which was published in 2000, but it was available before that.**

Q. **Does the Handbook of Pharmaceutical Excipients describe individually all the excipients in claim 30 and 37 of the '857 patent?**

A. **Yes, it does.**

Q. **And does the Handbook of Pharmaceutical Excipients include recommended amounts for the excipients in claims 30 and 37 of the '857 patent?**

A. **Yes, it does.**

Q. **Prior to March 3rd, 2015, would a POSA have been motivated to develop a high load solid tablet formulation of ibrutinib?**

A. **Yes.**

Q. **And why is that?**

A. **Well, because, you know, it is well established within the pharmaceutical industry that you have capsules and you always go ahead and make tablets. Especially in this case,**

because as I described earlier, patients have to take four capsules each of 140 in order to have 560-milligram dose, which is necessary for the treatment.

So in a situation like that, of course, a POSA would be motivated to make a tablet which would have just single dose, single tablet with other doses.

Q. **So would a POSA be motivated to develop tablet dosage units contain more than 140 milligrams?**

A. **Yes.**

Q. **And why is that?**

A. **Because, you know, so to help patients for improving patient compliance and also making tablets is easier, cheaper and faster.**

Q. **Now, if a POSA thought to make a high load solid tablet formulation of ibrutinib prior to March 3rd, 2015, where would he begin?**

A. **Well, the starting point would be what is already out there, so they would look at the capsule and they try to compress it. If it doesn't compress, they start adding one or two excipients which are known to have compressability and that is how they start.**

They also look at what is available, what other sources of literature are there. They would also look at that. It is a routine experimentation.

Q. **And what do you mean by routine experimentation?**

A. **Routine experimentation is just that you have your capsules, you have your active drug and already excipients which are accepted by FDA. They are compatible. There is no issue there.**

So you start modifying the dose to see if you can continue making the tablet. You can also look at the literature. Prior to 2015, there's other literature like '172, like 2014, they already have described tablet formulations. You use those information and you proceed and you make your tablet.

Q. **Now, when you said 2014, were you referring to Goldstein 2014?**

A. **That's correct.**

Q. **Earlier you had discussed glidants. Would a POSA have been motivated to use a glidant in consideration with a formulation containing ibrutinib and the four excipients disclosed in the Imbruvica capsules?**

A. **For the reasons that I mentioned, when we make tablets, the speed of tablet production is high, so every POSA would know that powder has to flow well and uniform. So a well-known glidant.**

Q. **Now, are powder flowability issues a concern for capsules?**

A. **Not really, because capsule production is very small and they don't need to be compared. So it's not the major**

issue.

Q. **Now, earlier you mentioned colloidal silicon dioxide is commonly used as a glidant.**

Was colloidal silicon dioxide used in an Imbruvica tablet formulation before March 3rd, 2013?

A. **Yes.**

Q. **Where is it used?**

A. **In Goldstein 2014. If you look at the Examples 2 and 3, in both of those colloidal silicon dioxide is one of the excipients which is used.**

Q. **Earlier you mentioned that microcrystalline cellulose as a filler that was used in Imbruvica capsules. Would a POSA have been motivated to only use microcrystalline cellulose is a filler in an Imbruvica tablet formulation?**

A. **Well, they would use that, but because tablets have to be consolidated, a POSA knows that consolidation and compaction is a necessity to make tablets, so they would look at other fillers which demonstrate good compatibility. Typically, that is lactose.**

Q. **Now, why would a POSA include lactose in his ibrutinib tablet formulation?**

A. **Similarly because to facilitate processing, compactability and make the formulation.**

Q. **Was there any literature that identified lactose in combination with microcrystalline cellulose in that**

ibrutinib tablet formulation?

A. **Yes. Goldstein 2014, Example 2 and 3. Both of them, they used microcrystalline cellulose and lactose.**

Q. **Any others?**

A. **I believe also in '172 publication, it is also in the examples here.**

Q. **And why would it have been obvious to select lactose instead of some other filler or use in combination with microcrystalline in an ibrutinib tablet formulation?**

A. **Well, the '172 publication is a Pharmacyclics publication. Goldstein also uses lactose. So these are the ones that they have usually have seen no issue with that, so they -- you know, that's why the POSA would consider lactose as desirable excipient to be added.**

Q. **Would a POSA have been motivated to use a particular form of lactose in making an ibrutinib tablet formulation?**

A. **Lactose monohydrate is known to be highly compressible and this information is actually in the Handbook of Pharmaceutical Excipients that describes that. So, yes, lactose monohydrate would be the ideal one.**

Q. **In addition to colloidal silicon dioxide and lactose, would a POSA be motivated to include any other excipients in a tablet formulation containing the four previously discussed excipients in Imbruvica capsules?**

A. **So as I mentioned, because tablets need to be bound**

together, a strong binder would have been considered.

Q. **Why would a POSA have been motivate to use a binder in an ibrutinib tablet formulation?**

A. **As I mentioned, you know, you wants to use your binder maybe to granulate, but at the same time, you provide a thread to the tablet formation and tablets are to be hard and consolidated, so binders are used.**

Q. **Would a POSA have used hypromellose or starch in an ibrutinib tablet formulation?**

A. **I mean, in the examples, they were used, but a POSA would also know that these are sources that is supplied and there's always impurities in there. For example, a starch: Rice, potato, tomato sauce, and so on. So they would rather go for a superior binder.**

Q. **And what kind of binder would they consider then instead?**

A. **They would consider, for example, a synthetic one, which would be like polyvinylpyrrolidone.**

Q. **And why would a POSA prefer to use a synthetic binder in an Imbruvica tablet formulation?**

A. **Well, it's more reliable. You know, the suppliers are consistently providing the same quality.**

Q. **Is PVP a commonly used -- when I say PVP, you understand I'm referring to polyvinylpyrrolidone?**

A. **Yes.**

Q. **Is PVP a commonly used binder in tablet formulation?**

A. **Yes, it is extensive use.**

Q. **Did any literature prior to March 3rd, 2015, identify PVP as a binder that is compatible with ibrutinib in an ibrutinib tablet formulation?**

A. **Well, prior to that, yes, because polyvinylpyrrolidone was used. And so what was the question exactly?**

Q. **Sure. Did any literature prior to March 3rd, 2015, identify a PVP as a binder that was compatible with ibrutinib in an ibrutinib tablet formulation?**

A. **Yes. I think the Pharmaceutical Handbook has that and also the published literature.**

Q. **And which published literature?**

A. **I believe it was in 2014.**

Q. **Goldstein 2014.**

A. **Yes, as well.**

Q. **Any other literature?**

A. **I believe the '172 also had it. I think I've seen it there as well.**

Q. **Having selected ingredients for use in an ibrutinib tablet formulation, what would a POSA do next?**

A. **Well, once the excipients are selected, then the POSA would proceed with manufacture.**

Q. **And how -- once you have the selection of excipients, how would you determine the amounts of excipients to use in**

a tablet formulation?

A. **Well, they would look back again at percentages that are used in the, both in '172 and in Goldstein 2014 and all the ranges that are provided in the Pharmaceutical Handbook and accordingly determine what percentage they should take and move forward.**

Q. **So would a POSA have any guidance with respect to the amount of lactose monohydrate to include an ibrutinib tablet formulation?**

A. **The Example 11 of the '172 publication, we can see Table 6, that they have used microcrystalline cellulose, and the range is 5 to 50 percent. Lactose, 10 to 75 percent. So those are the two ranges, and, of course, within those ranges, you can pick one that helps you develop your formulation.**

Q. **And that's DTX-1399?**

A. **That's correct.**

Q. **Would a POSA have any guidance with respect to the amount of microcrystalline cellulose to includes an ibrutinib formulation?**

A. **Yes.**

Q. **And --**

A. **So the range is 5 to 50 percent.**

Q. **And where was that disclosed in the art?**

A. **Again, in Example 11, the formulation and components**

are there and in the range on the table indicates 5 percent to 50 percent for microcrystalline cellulose.

Q. **Would a POSA have any guidance with respect to the amount of croscarmellose sodium to include an ibrutinib tablet formulation?**

A. **Again, Example 11 would provide 0 to 15 percent for croscarmellose sodium.**

Q. **Would a POSA have any guidance with respect to the amount of magnesium stearate is included in an ibrutinib tablet formulation?**

A. **Yes. In same Example 11, the magnesium is in the range of .25 percent to 2.5 percent.**

Q. **Would a POSA have any guidance with respect to the amount of colloidal silicon dioxide to include in the tablet formulation?**

A. **Yes. This is a slide from the copies of excerpt from Pharmaceutical Handbook. The first one is colloidal silicon dioxide. It mentions in the table .1 to .5 percent is the range.**

Q. **And that is DTX-1625?**

A. **That's correct.**

Q. **Would a POSA have any guidance with respect to the amount of polyvinylpyrrolidone to include in its ibrutinib tablet formulation?**

A. **Yes. Again, polyvinylpyrrolidone is mentioned there.**

This is just excerpt from there and it describes the binder for the lower part of the table, .5 to 5 percent would be amount of binder that can be used.

Q. **Would a POSA have any guidance with respect to the amount of sodium lauryl sulfate to include in an ibrutinib tablet formulation?**

A. **Yes. Again, excerpt from the Pharmaceutical Handbook. It describes ranges for sodium lauryl sulfate. So if you want to use it to help solubilization, one to two percent is mentioned.**

Q. **Now, as of March 3rd, 2015, would a POSA have been motivated to use a particular dose amount of ibrutinib in the ibrutinib tablet formulation?**

A. **Sure. I think --**

Q. **What would that be?**

A. **The 560, as I mentioned earlier. That -- the point of movement, because you have a capsule and you want to create a high load formulation, 560, so that is what we used.**

Q. **And is 560 mgs disclosed in the prior art?**

A. **Yes.**

Q. **And what prior art is that?**

A. **Well, Imbruvica capsules, it's required for a patient to be taking once a day.**

Q. **Now, prior to March 3rd, 2015, would a POSA have a motivation to combine Imbruvica's 2013 label with a '172**

publication, Goldstein 2014, and the Handbook of Pharmaceutical Excipients?

A. **Sure. That is a very obvious approach, yes.**

Q. **And why is that?**

A. **Well, because you are looking at prior art, what is available, and so you look at what is approved by FDA, such as Imbruvica capsules. Then you want to make tablets, so you do your own routine experimentation and if you need more information, you look at publications such as '172, which describes the tablets, Goldstein, which describes the tablets and also Pharmaceutical Handbook, which is well-known and routinely used for selection of excipients.**

Q. **And which of those references relates to the Imbruvica formulation?**

A. **Imbruvica 2013. That is the label we talked about earlier.**

Q. **Any others?**

A. **Also the 172 publication describes the tablet of Imbruvica. So does Goldstein 2014. Ultimately, they have, they have the active ingredient in them.**

Q. **Well, prior to March 3rd, 2015, would a POSA have had a reasonable expectation of success in making a high load solid tablet formulation?**

A. **Yes, they would have had that expectation, yes.**

Q. **And why is that?**

A. **Well, because already capsules were available and approved by FDA. Pharmacyclics, you know, they used excipients that they published in the '172 and all the prior art, which are described shows that they are all easy to use. There is no issue. So, yes, expectations would have been successful.**

Q. **Was Pharmacyclics the only pharmaceutical company to develop an ibrutinib tablet?**

A. **No. It was also I believe the Goldstein bio, bio pharma, I forget the name, but they also described it, described the tablet, yes.**

Q. **I think you're referring to Principia Biopharma?**

A. **That's correct. Thank you.**

Q. **And would a POSA have a reasonable expectation of success in making a high load solid tablet formulation containing the claimed ingredient at the claimed amounts?**

A. **Yes.**

Q. **And why is that?**

A. **Well, because the high load formulation was already disclosed in the, as I showed you in the earlier, about 80 percent in one formulation of Goldstein, and also in the other formation in '172, so it was all there. Components were there. And, yes, a POSA would have been able to deliver the formulation and good expectation of success.**

Q. **Now, let's shift gears a little bit. What is a**

Maillard reaction?

A. **A Maillard reaction is basically reducing a sugar, one of them being lactose. When they come in contact with a strong amine and different conditions, such as high temperature and pH, they might react. So that is Maillard reaction.**

Q. **Is ibrutinib an amine containing compound?**

A. **It has an amino group, but it is a very weak amino group. So nothing has been said about its potential and compatibility because already the Pharmacyclics publication, they used lactose. Goldstein used lactose and there was no issue.**

Q. **So a POSA would not have any concerns with combining that ibrutinib with lactose and making an ibrutinib tablet formulation?**

A. **No, because it doesn't react like lactose.**

Q. **So to summarize, is it your opinion that claims 30 and 37 of the '857 patent are obvious in view of the prior art?**

A. **Yes.**

Q. **Now, I just want to shift gears briefly to your lack of written description argument.**

Do claims 30 and 37 of the '857 patent identify a mass amount of ibrutinib that can be included in the claim formulation?

A. **Well, I have to refer to the slide. So here, the two**

claims, 30 and 37. So claim 37 depends on claim 27, and in there, there's a mass amount which is designated. If you look at below the chemical structure of the, of claim 27, you will see there an amount of about 70 milligrams to about 840 milligrams is mentioned. So that is the mass amount for that.

As far as claim 30 is concerned, there is no mass amount, only percentages, and that means it applies to all masses, because they have not given any mass. So they say 70 percent weight by weight of the ibrutinib and that means all the strengths can be made.

Q. **Do claims 30 and 37 of the '857 patent encompass solid tablet formulations containing 140 mgs and 560 mgs ibrutinib?**

A. **No.**

Q. **And -- well, let's take a look again. Earlier you mentioned they covered 70 to 840 mg. We'll take it step by step for claim 37.**

A. **I'm sorry. Yes.**

Q. **And so my question is: Claim 37 contain 140 and 560 mgs ibrutinib?**

A. **You describe that milligram quantity in there, so it doesn't spell it out. So that is the range that is mentioned.**

Q. **And does it fall within that range?**

A. **I think 140 and 560 fall in that range.**

Q. **And earlier you mentioned that there was no range in claim 30 and so that it covered all ranges.**

A. **That's correct.**

Q. **And so would claim 30 then include a tablet formulation containing 140 mgs and 560 mgs ibrutinib?**

A. **No.**

Q. **And --**

A. **Because I don't have the mass amount.**

Q. **Okay. So let me ask the question a little differently. So you mentioned that claim 30 doesn't have the specific range of ibrutinib, the amount, and so you mentioned that it covered all ranges, mgs dosage amount?**

A. **Yes.**

Q. **And so my question is: So that would include, would that include 140 mgs or 560 mgs of ibrutinib?**

A. **Yes.**

Q. **And does claim 30 and 37 include amounts of ibrutinib other than 140 and 560 mgs?**

A. **No, they do not.**

Q. **So let's break it down again.**

So in claim 37, where it mentions that it's a range from 70 to 840 mg ibrutinib, does that range include ranges of ibrutinib -- include amounts of ibrutinib other than 140 and 560? Well, yes. It is, it is a range from 70

to 840. Yes, it does.

Q. **And with respect to claim 30, you mentioned it could cover all ranges. So it would include tablet formulations that contained ibrutinib in the amount of other than 140 and 560?**

A. **Yes.**

Q. **Do you think the '857 patent as a guide, does the specification describe solid tablet formulations containing any amount of ibrutinib other than 140 or 560 mgs?**

A. **No, it doesn't indicate anything beyond those two.**

Q. **Does Example 1 disclose solid tablet formulations containing any amount of ibrutinib other than 140 or 560 mgs?**

A. **No.**

Q. **Does Example 5 disclose solid tablet formulations containing any amount of ibrutinib other than 140 or 560 mgs of ibrutinib?**

A. **No.**

Q. **Before March 3rd, 2015, would a POSA have understood the '857 patent discloses solid tablet formulations containing any amount of ibrutinib other than 140 or 560 mgs?**

A. **No.**

Q. **Are you aware that the '857 patent contains a photo of solid oral, of solid oral formulations?**

A. **Yes. I've seen that, yes.**

Q. **That's Figure 3 of JTX-10?**

A. **Yes.**

Q. **Does Figure 3 of the '857 patent disclose solid tablet formulations containing 140 mgs, 280 mgs, 420 mgs and 560 mgs of ibrutinib?**

A. **No.**

Q. **And does the photo indicate what the contents of those tablets are, and B and E through Figure 3?**

A. **There is no description of formulation there, no.**

Q. **To summarize, based on everything you have seen and reviewed in the specification of the '857 patent, would a -- does the patent, does the '857 patent demonstrate to a POSA before March 3rd, 2015, that the listed inventors were in possession of solid tablet formulations containing any amount of ibrutinib other than 140 or 560 mgs?**

A. **No.**

MR. HANNA: I will pass the witness.

THE COURT: It's 5:00 o'clock, so we'll call it a day.

All right. Thank you, Mr. Hanna. It's 5:00 o'clock. We're getting ready to call it a day. Let's just briefly talk time.

So, Doctor, you're excused for the day. I guess you'll be back Monday.

Mr. Sipes, do you intend to cross-examine the witness?

MR. SIPES: I had planned to do a little cross-examination, Your Honor.

THE COURT: We'll see you then, Dr. Fassihi. We're going to begin on Monday at 8:30. All right?

And the lawyers just want to stick around. Thank you, Doctor. Have a good weekend.

THE WITNESS: Thank you.

THE COURT: We'll see you Monday.

(Witness excused.)

THE COURT: And then let's talk about time. I believe there have been communications between counsel and my deputy clerk and/or case manager, and I understand that day three was broke down as follows: Three hours 11 minutes for plaintiffs. Four hours, 47 minutes for defendants. So leaving us for the first three days a total of eight hours and 42 minutes expended by, if that's the right word, by plaintiffs, 15 hours, 10 minutes by defendants.

Now, I don't have the debts broken down in the specifics that I have, Ms. Clayton, but I'm going to stick to the 10.5/16.5 breakdown. Where do defendants -- unless the defendants have agreed to some alternative arrangement.

MS. CLAYTON: I think that's the plan that we still have right now, Your Honor. We'll confer with Alvogen

over the weekend if we think we can give them more time.

I think on that breakdown --

THE COURT: Well, just keep in mind when I say that, you know, you're free to do whatever you want. You can be courteous. That's great and generous as you might want.

I'm going to benefit from some closing arguments and I told you all that in terms of planning for your trial. And everybody has to bear the consequences of the decisions they make about how they want to try their case. And I have already indicated, I mean, I think things could have been quicker with some of the experts. And this last thing is a great example. I mean, you know, you don't need to keep repeating questions about, to make your point when a single question often will do it.

So I will say based on the manner in which the evidence has been adduced, I am confident that 27 hours was more than enough for both sides to try their case, especially with Zydus' departure, and I'm very confident it's an eminently fair distribution between the two defendants to say that Alvogen was given 16.5 and defendants were given 10.5.

MS. CLAYTON: Your Honor, I think we've calculated thus far Sandoz has used six hours and 18 minutes. Is that correct? And so whatever the

difference is there and I'm a little tired, so my brain is not going to be able to have me do that math quickly. Whatever the balance is, that's the time that would be attributable to Alvogen.

THE COURT: Okay. You guys can work that out over the weekend. We've got numbers here. If there's a dispute, you let me know, but all three parties, I will remind them that I do think I would benefit from narrowly focused closing arguments. Okay? All right.

MR. SIPES: And, Your Honor, you know, as the plaintiff, we've grown increasingly concerned, here we are on Friday. We have yet to start our response to their invalidity case. A lot of this is out of our hands. They tell us even after Dr. Fassihi, they have another witness to call.

THE COURT: Okay. But, wait. Mr. Sipes, I guess I'm confused. You have got plenty of time left to try your case. Right?

MR. SIPES: Yes. I just want to make sure -- we're going to calculate over the weekend that there remains enough time through Wednesday afternoon.

THE COURT: But I calculated -- oh, because you're -- look, built into the schedule is more than 27 hours per side.

MR. SIPES: Okay.

THE COURT: Right? I mean, we've got Monday, Tuesday and Wednesday scheduled. I mean, we've got, you know, 17 hours scheduled for Monday and Tuesday. I mean, the defense only has -- I mean, ballpark today, do you think they've used six today, five?

MR. SIPES: That's probably about right.

THE COURT: So that means that at the end of today, they only have, you know, five-and-a-half to six hours or so left for their entire case.

MR. SIPES: Right. All right, Your Honor. I got it. We look forward to starting our case. Thank you, Your Honor.

THE COURT: Okay. Anything else?

MR. HANNA: Yes. I have exhibits I'd like to enter in for Dr. Swift yesterday.

THE COURT: Why don't you do that, confer over the weekend, make sure it's all streamlined. That's an example, if you all agree to it, just give me something in writing. We will just put it in the record in evidence and save time.

MR. HANNA: Yes, Your Honor.

MS. CLAYTON: Sounds good, Your Honor.

THE COURT: And, Ms. Clayton, I might be inferring too much. If you are afraid of time, you let me know. I do think you've not unduly taken time and I don't

want your client to be prejudiced.

MS. CLAYTON: I think with the time we have left, Your Honor, it won't be a problem, but if I become concerned, I will let you know.

THE COURT: Anything else? Everybody have a good weekend. I will see you Monday morning. Thank you.

MR. SIPES: Thank you.

MS. CLAYTON: Thank you.

(Court recessed at 5:10 p.m.)

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